

The University of Chicago

A STUDY OF ALKALOSIS WITH SPECIAL
REFERENCE TO THE ELECTROLYTE
COMPOSITION OF THE BLOOD
SERUM AND THE ROLE
OF THE KIDNEY

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
BIOLOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF MEDICINE

1942

By

JOSEPH B. KIRSNER

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PREFACE

The impetus for this work was the desire to study the alkalosis encountered clinically during the antacid treatment of peptic ulcer and during pyloric obstruction. It was hoped that, with a better understanding of the mechanisms involved, more satisfactory methods for prevention and therapy could be devised.

The fact that severe alkalosis may develop from the administration of alkalis, or from pyloric obstruction with continued vomiting has long been known. Attention has been centered in this work on these two types of alkalosis. A survey of the clinical records of patients receiving antacid therapy was made in order to gain a better general understanding of the problem. Experimental studies in animal and man were then carried out in order to clarify certain aspects. These investigations included observations on mineral excretion, renal function, and alterations in serum electrolytes under various conditions. Histologic studies of the kidney were carried out both in the experimental animal and in man. The various phases of the work will be presented separately and a correlation attempted at the end.

The author wishes to express his deep gratitude to Dr. Walter Lincoln Palmer, who first suggested this problem, and whose constant encouragement and counsel made the investigation possible. He wishes to acknowledge the valuable aid given by Drs. Louis Leiter, George G m ri, and Eleanor Humphreys in the interpretation of the histologic findings described in Part VII, and also the co-operation shown by Dr. Kathryn Knowlton in carrying out the majority of the determinations of serum electrolytes in the patients studied.

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PART I. ALKALOSIS COMPLICATING THE SIPPY TREATMENT
OF PEPTIC ULCER

A Clinical Analysis of 135 Episodes

Accepted for publication, Archives of Internal Medicine

INTRODUCTION

Between 1929 and 1939 approximately 1350 patients with peptic ulcer were treated at the Albert Merritt Billings Hospital by the Sippy program. This regimen included the frequent use of milk and cream and soft foods, nightly aspiration of the gastric contents, and the hourly administration of alkali. The combinations of alkali used were:

1. Calcium carbonate 0.6 gms., sodium bicarbonate 2.0 gms.;
2. Calcium carbonate 1.2 gms., sodium bicarbonate 2.0 gms.;
3. Calcium carbonate 2.0 gms., sodium bicarbonate 2.0 gms.

Magnesium oxide 0.6 gms. and sodium bicarbonate 0.6 gms. were employed to regulate bowel activity. Thirty-two grams of sodium bicarbonate and from 10 to 32 gms. of calcium carbonate thus were administered daily. The protein intake in these patients varied from 35 to 40 gms. daily for the first few days; as feedings were added the protein intake was increased rapidly to 65 gms., and after two weeks averaged from 75 to 80 gms. daily. Alkalosis, as indicated by an alteration in the acid-base balance, was observed in 135 episodes in 111 patients.¹ The series comprises 117 men and 18 women of ages ranging from 20 to 79. The high incidence of males follows the usual sex distribution of ulcer in our patients of about 6 to 1.

METHOD OF STUDY

Acid-Base Balance

Determinations were made of the serum CO_2 , pH, and chloride, and of the blood urea nitrogen at variable intervals during therapy (1). Alkalosis is characterized chemically by an elevation in the serum CO_2 and pH. In this study, the degree of the

¹For the purpose of clarity, the 135 instances of alkalosis will be referred to as 135 patients, since the multiple episodes of alkalosis in 18 patients each occurred during separate hospital admissions. The incidence of alkalosis in this study cannot be determined since electrolyte studies were not obtained routinely in all the 1350 patients.

acid-base disturbance was evaluated and classified on the basis of these alterations in the electrolyte balance. The relationship of the individual changes to each other was not studied (see Hastings [3] and Eisele [4]) but rather the total alteration in serum electrolytes and in renal function as indicated by the urea clearance test.

Renal Function

Routine examinations were made of the urine in all cases and, in addition, renal function was measured by the urea clearance test of Van Slyke (2). The urea clearances were carried out in the hospital and in the Out-Patient Clinics. The analyses were made by trained laboratory assistants under the direction of a chemist, Dr. Kathryn Knowlton, but not by her directly, by ourselves, or by research chemists. Nevertheless, we believe the determinations to be quite reliable and to constitute at least a satisfactory "first approximation." The urea clearance test is not an absolute measure of renal function. It may be influenced by various extrarenal factors such as dehydration, a low output of urine, and by the protein content of the diet. Rather widely variable results have been noted in presumably normal individuals. However, the urea clearance test, when carefully performed, is probably superior to such tests as the phenolsulphonphthalein excretion and the sulphate clearance. Values of 75% or more of average normal were considered normal; those between 55 and 75% were arbitrarily classified as slightly reduced, while values below 55% of average were accepted as definitely low. The results are interpreted chiefly as an indication of the trend of renal function in relation to alkalosis. They do not define the nature of the renal disturbance.

RESULTS

Clinical Aspects

As may be seen from Table 1, a slight alkalosis occurred in 71 patients, a moderate alkalosis in 27, and a severe alkalosis in 37. The range of serum chloride, CO_2 , and pH are noted in the table. The incidence of alkalosis according to age decades is shown in Table 2. As was to be expected, most of the patients were between 30 and 60 years of age. It will be noted also that

the incidence of moderate and severe alkalosis increased in the older age groups. Alkalosis appeared more than once in 18 patients (Table 3); twice in each of 13 individuals, and three times in each of five cases. Renal function prior to this complication had been normal in five patients and slightly reduced or low in nine (undetermined in four). It has been noted frequently that, after recovery from alkalosis, the administration of alkali may subsequently be resumed without difficulty and without chemical alkalosis. This phenomenon was observed in 29 of the present series (Table 4). The ingestion of alkali was resumed without the development of symptoms by many more patients but chemical studies were not made.

There were four deaths in this series attributable to the syndrome of alkalosis, hypochloremia, and dehydration. In all of these there was persistent vomiting secondary to pyloric obstruction. The necropsies performed in the four cases are described in Part VII.

The symptoms of alkalosis usually appeared between the fourth and tenth days of treatment, although in some patients not until after several weeks had elapsed. The earliest complaints were a distaste for the milk and cream and alkali, followed by weakness, dizziness, headache, dryness of the mouth, nausea and vomiting. Nervousness, clouding of the mentality, and changes in personality were occasionally observed; these manifestations progressed in a few instances to actual coma. Muscular twitchings and hyperactive reflexes were noted infrequently. Two patients described a persistent aching in the jaws and teeth although no dental condition could be detected. Tetany associated with a positive chvostek sign and mild convulsions appeared in only one patient; the alkalosis in this case had been intensified by persistent vomiting secondary to pyloric obstruction. These manifestations disappeared with varying rapidity after the administration of adequate quantities of sodium chloride and water. It should be noted that the majority of patients with slight alkalosis and several with moderate or severe alkalosis did not exhibit any symptoms, the condition being detected only by routine chemical determinations. There was not a direct relationship between the severity of symptoms and the degree of alkalosis, or between the quantity of alkali administered and the frequency of the condition. It occurred in a 29-year-old man after the admin-

istration of 27 gms. of calcium carbonate and 90 gms. of sodium bicarbonate respectively in three days, whereas the acid-base balance remained normal in a 25-year-old man receiving the same daily dosage for 54 days (total intake--calcium carbonate 654 gms., sodium bicarbonate 1620 gms.).

Contributory Factors

1. Massive Hemorrhage

Jordan and Kiefer (5), Bockus and Bank (6), and Jeghers and Lerner (7) have suggested that massive hemorrhage may increase the tendency to alkalosis. It is of interest to note, therefore, that in the present series (Table 5), hemorrhage had occurred in 60 of the 135 cases. The alkalosis was slight in 34 instances, moderate in 13, and severe in 13 patients. On the other hand, the acid-base balance remained normal during alkali therapy in a group of 38 patients with hemorrhage not included in the present study. There was no direct correlation between the severity of the bleeding and the frequency of alkalosis.

2. Hypochloremia

The role of hypochloremia in the development of alkalosis has not received sufficient emphasis heretofore. Chloride deficiency in ulcer patients may result from the low intake of salt which varies from 1.5 to 2.5 gms. daily instead of the usual 10 to 12 gms., from vomiting, and from the nightly aspiration of the gastric contents. The loss of chloride by this latter route is of particular significance in patients with gastric retention and is frequently associated with marked dehydration. Gastric retention, as evidenced by the nightly aspiration of more than 200 cc. of gastric content, was present in 6 of the 71 patients with slight alkalosis (8.5%), in 10 of the 27 patients with moderate alkalosis (37%), and in 20 of the 37 cases with severe alkalosis (54%). The importance of gastric retention is further indicated by the fact that it was present in 25 of the 55 patients of the present series in whom the blood urea nitrogen increased during alkalosis. The absence of alkalosis in many individuals receiving alkali and consuming a salt-poor diet suggests that the development of hypochloremia may be determined by individual varia-

tions in the fluid balance and salt reserve of the body prior to treatment.

3. Antecedent Renal Disease

(a) Renal function before alkalosis.--Many writers (8, 9, 10, 11, 12) have noted a definite correlation between the incidence of alkalosis and the presence of renal disease, although few studies have been made of renal function prior to the acid-base disturbance. Eisele obtained suggestive evidence of pre-existing renal damage (as shown by the blood pressure, presence of anemia, arteriosclerosis, and prostatism) in 19 of 28 patients. Wilkinson and Jordan (13), using the sulfate clearance, noted precedent renal impairment in a large number of cases later developing alkalosis. Alkalosis, nevertheless, may appear in the absence of renal impairment (14, 15, 16) and often does not occur in persons with renal disease (7, 10, 15, 17, 18). Gatewood, Gaebler, and Muntwyler (19), and Cope (20), could find no evidence of antecedent renal disease in the majority of their patients.

In the present study, 16 episodes of alkalosis occurred in individuals with genito-urinary disease (Table 6). Among these, nephrolithiasis was present in five, ureteral calculus in six, recent pyelitis in two, and bilateral ascending suppurative nephritis, chronic nephritis, and multiple urethral strictures in the remaining three patients respectively. On the other hand, the acid-base balance was undisturbed in a group of 23 similar patients receiving alkali. This group comprised ten patients with nephrolithiasis, eleven with ureteral calculus, and one each with post-transfusional nephropathy and renal tuberculosis. The initial urea clearance was normal in three of nine patients with renal disease developing alkalosis as compared with normal clearances in 10 of 16 patients not developing alkalosis.

Thirty-seven of the 135 episodes of alkalosis occurred in patients with hypertension (Table 7). The urea clearance at the onset of treatment had been normal in 7, and reduced or low in 14 of this group (undetermined in 16). Alkali therapy has been used rather routinely in hypertensive patients with ulcer but adequate electrolyte studies are available in only 17 of those who did not develop symptoms of alkalosis. Renal function at the onset of treatment had been normal in 7 and low in 8 of this group (undetermined in 2).

The effect of alkalosis upon the urea clearance was studies in 48 patients of the present series.¹ Renal function at the onset of alkali therapy was normal in 24 cases, reduced in 8, and low in 16 (Table 8). A normal clearance was obtained prior to alkalosis in 12 of 23 patients with slight alkalosis, in 8 of 13 with moderate alkalosis, and in 4 of 12 patients with severe alkalosis.

(b) Renal function during alkalosis.--Urea and sulfate clearances, as well as the excretion of phenolsulphonephthalein, have been found reduced during alkalosis by various workers (13, 21). The mechanism by which the decrease is brought about and the nature of the renal lesion are not known. McCance and Widdowson (21) observed a fall in creatinine, sucrose, inulin, and urea clearances in a patient with alkalosis resulting from pyloric obstruction, and suggested that the major dysfunction was a decrease in glomerular filtration. The impaired renal function also has been related to dehydration with its attendant consequences. In the present study, the urea clearance was determined during alkalosis in the same 48 patients considered above (Table 9). No change in renal function was noted in 20 cases. In 14 of these the original urea clearance had been normal. In the 28 instances in which renal function decreased, the change was arbitrarily considered as slight² in 4, moderate in 11, and marked in 13 cases. Renal function originally had been normal in 10 and reduced or low in 18 patients of this group. The urea clearance decreased most frequently during severe alkalosis and apparently more often in patients with antecedent impairment of renal function. Thus, a diminution occurred in 10 of 24 cases in which a normal clearance had previously been obtained, whereas a decrease occurred in 18 of 24 cases in which the initial clearance had been low.

¹Urea clearances were obtained at the onset of alkali therapy in 25 additional cases; these data are omitted from the present discussion because renal function was not measured during the period of alkalosis.

²Slight change estimated as a reduction of 15 to 25% of average normal; moderate change estimated as a reduction of 25 to 45% of average normal; marked change estimated as a reduction of 45% or more.

The change is considered as a decrease from normal to low levels or to an indicated decrease within range of lowered clearance values.

(c) Renal function shortly after alkalosis.--The status of renal function shortly after alkalosis seems to have been determined only occasionally by other workers. Jeghers and Lerner observed one case in which there was evidence of renal impairment four months after restoration of a normal acid-base balance. Berger and Binger noted decreased function in five of seven patients several weeks after alkalosis. Binger, Hastings, and Neil (22) administered 5.7 gms. of sodium bicarbonate to a patient for 35 days; alkalosis resulted but there was no evidence of damage to the kidneys other than a slightly reduced phthalein excretion. Cope reported the case of a man who had experienced four severe attacks of alkalosis; the urea clearance after recovery from the fourth episode was 92%. Normal function after alkalosis has been reported also by Gatewood, Cooke, and others.

In the present series, of 28 patients in whom, as mentioned previously, the urea clearance fell during alkalosis, further determinations were made in 22 within several weeks after the episode (Table 10). The clearance returned to its previous level in 19 of the 22 patients shortly after the alkalosis. The original values had been normal in 6 and reduced or low in 13 of this group. In the three patients in whom the clearance was below its initial level shortly after the alkalosis, the original function had been normal in two and low in one (Table 11). It should be noted that the urea clearance later returned to its original level in all three of these patients.

It is evident, therefore, that alkalosis does not cause a persistent diminution of renal function, although in occasional patients a decreased urea clearance may be demonstrable for at least several months.

4. Blood Urea Nitrogen

The blood urea nitrogen often rises markedly during alkalosis and returns to normal with recovery. The blood creatinine, inorganic phosphate, and inorganic sulphate may do the same. In the present series, the blood urea nitrogen increased in 17 of the 71 episodes of slight alkalosis (24%), in 13 of the 27 instances of moderate alkalosis (48.1%), and in 25 of the 37 episodes of severe alkalosis (67.5%) (Table 12). The highest blood urea nitrogen values occurred in patients in whom there was evidence of primary renal disease. The high incidence of other com-

plications is of interest; hemorrhage was present in 16, hypertension in 16, and gastric retention in 25 cases. In this connection it should be emphasized that an elevation in the blood urea nitrogen does not, per se, indicate intrinsic renal disease (cf. Part VI).

5. Urine

Although the presence of albumin, casts, and red blood cells in the urine during alkalosis has been reported frequently (7, 8, 17), this finding was uncommon in the present series. A trace of albumin was detected in the urine of four patients with slight alkalosis, in seven with moderate alkalosis, and in ten with severe alkalosis. A moderate amount of albumin was found in the urine of two patients with moderate alkalosis. Hyaline and granular casts were noted in one individual with moderate alkalosis, and in another with severe alkalosis. Both albumin and casts were present in the urine of three patients during severe alkalosis. Gross or microscopic hematuria was not observed.

Treatment

The treatment of alkalosis is simple and effective. It consists of the discontinuance of alkalis, the administration of either ammonium or, preferably, sodium chloride, in amounts varying from 5 to 15 gms. daily, and the administration of large amounts of water by mouth or by clysis. Parenteral fluids, such as normal saline or 2% saline, may be necessary to combat the hypochloremia in the more severe forms of alkalosis. Although the use of 5% glucose in distilled water is of great value as supplemental therapy to relieve the dehydration, nevertheless normal saline solution is to be preferred for it replaces both the lost chloride and the water. The treatment of alkalosis in the present series is summarized in Table 13.

Pyloric obstruction ultimately necessitating surgical intervention was present in the majority of the cases requiring the administration of parenteral fluid. Clinical and chemical improvement rapidly ensued after the institution of these therapeutic measures; the acid-base balance usually was re-established within two or three days after the use of parenteral fluid and within five to seven days in patients receiving salt and fluid by mouth.

The Effect of Prolonged Alkali Therapy with and
without Alkalosis on Renal Function

There have been few studies of renal function after prolonged alkali therapy. Gatewood and Myers (23) found no evidence of renal damage after the use of alkali in a series of 46 patients; the total intake of sodium bicarbonate, calcium carbonate, and magnesium oxide averaged 30 gms. daily. Gatewood (19) reported similar results in another study in which renal function was estimated by the phenolsulphonaphthalein excretion test. Berger and Binger (10) observed one patient who took massive quantities of sodium bicarbonate and calcium carbonate for many years without developing renal impairment. Steele (24) reported the case of a 52-year-old man who had taken alkali for 14 years. The urine contained albumin and casts, the blood urea nitrogen was elevated, and the ability of the kidneys to excrete urea and to concentrate urine was markedly reduced. The blood urea nitrogen returned to normal six months after alkali was discontinued and the power of the kidney to concentrate urine rose slowly to normal during a period of two years. Hyaline casts and red blood cells continued in the urine, and faint traces of albumin appeared occasionally. The interpretation of this case is somewhat difficult; the continued presence of hyaline casts, albumin, and red blood cells suggests that pre-existent renal disease may have been present and possibly further aggravated by the alkali. The concentrating and excretory powers of the kidney were eventually restored, thus indicating that no irreversible injury to the kidney had occurred.

Evidence bearing on the effect of prolonged alkali therapy on renal function was obtained in 62 patients (Table 14). The cases may be divided into two groups: (a) those without alkalosis at any time and (b) those in whom alkalosis occurred.¹

Group (a) includes 29 patients, 25 males and 4 females, of ages ranging from 26 to 65 years (average 44 years). Alkali had been used previously by 28 of this group. The initial urea clearance was normal in 18. The follow-up period varied from 6 to 12 months in two individuals, from one to five years in 21, and from six to nine years in six patients. During the period of

¹This group is included in the series of patients discussed previously.

observation varying quantities of alkali were taken by all 29 patients. The final urea clearance was unimpaired in 28 of the 29 patients. The only case in which the urea clearance seemed to be definitely lowered was that of a 68-year-old woman in whom, after the ingestion of large quantities of alkali for five and one-half years, the urea clearance decreased from 67% to 40% of average normal. The initial clearance of 67% was obtained at a time when, upon admission to the hospital, dehydration was present as a result of continued vomiting. The blood urea nitrogen was 36.2 mg.%. In the subsequent five and a half years the patient has taken large quantities of alkali and has remained well clinically. The urea clearance measures 40% (two determinations--maximum clearances); the blood urea nitrogen is normal. There has been no elevation of the blood pressure. The urine does not contain albumin or casts, and its specific gravity occasionally exceeds 1.020. Thus, there is no conclusive evidence of renal injury in any of the 29 cases even though four of them had pyloric stenosis, two had hypertension, and one had a post-transfusional nephropathy.

These results indicate that prolonged alkali therapy, uncomplicated by alkalosis, does not impair renal function either in patients with normal urea clearances or in persons with pre-existing renal impairment.

Group (b) consists of 33 patients, 27 males and 6 females, of ages ranging from 25 to 71 (average 49 years), all of whom had taken alkali previously. The initial clearance was normal in 14 of these cases. The period of observation extended from two to 12 months in 6 patients, from one to five years in 19, and from five to ten years in 8 cases. During this time varying amounts of alkali were used by 30 patients of the group. Alkalosis had occurred on 48 occasions. The final urea clearance was unimpaired in 31 of the 33 cases. Renal disease was present in 6 patients of this group, gastric retention in 11, and hypertension in 6. A decrease in the urea clearance was observed in two patients:

Case 1.--G. W. (Unit no. 78083), a 47-year-old housewife, had experienced ulcer symptoms for three and a half years. She had known for eight months that her blood pressure was elevated. The important physical findings on admission to the hospital were pallor of the skin, obesity, and slight enlargement of the heart. The blood pressure was 150 systolic and 100 diastolic. Roentgen studies revealed a stenosing duodenal ulcer. One hundred and

thirty-five grams of calcium carbonate and 450 gms. of sodium bicarbonate were given in 15 days (2/28/33 to 3/14/33). The acid-base balance remained normal; the urea clearance was 85% of average normal and the blood urea nitrogen 7.9 mg.%. Moderate quantities of alkali were taken by the patient for the next seven months. She then re-entered the hospital (10/10/33 to 10/24/33) and received 96 gms. of a mixture of sodium citrate and tribasic calcium phosphate in two days. The blood pressure was 178/108. Because of marked pyloric stenosis, a posterior gastroenterostomy was performed from which the patient made an uneventful recovery. Small amounts of alkali were taken during the subsequent nine months until July 23, 1934. The patient was then not seen by us until May 15, 1936, at which time she was hospitalized because of a severe hemorrhage from a jejunal ulcer (5/15/36 to 6/5/36). The blood pressure was 152/90. Seventy-eight grams of calcium carbonate and 160 gms. of sodium bicarbonate were given in the first five days. Because of recurrent hematemesis, the alkali was discontinued for the next three days during which time normal saline solution was administered parenterally. Alkali therapy then was resumed, the patient receiving a total of 570 gms. of the sodium citrate, tribasic calcium phosphate mixture in 11 days. There was no significant alteration in the acid-base balance; the blood urea nitrogen was 12.9 mg.%. Two months later the patient again entered the hospital because of a recurrent massive hemorrhage (8/16/36 to 10/11/36). The blood pressure was 160/105. Two blood transfusions were given, and on the fifth day the gastroenterostomy was taken down. Wangensteen aspiration was required for eight days postoperatively; in addition to parenteral fluids, therapy also included the use of the Winkelstein drip for eight days. Convalescence was complicated by the development of a coronary occlusion two weeks after the operation. The patient recovered, however, and received 90 gms. of calcium carbonate and 330 gms. of sodium bicarbonate in eleven days. A moderately severe chemical alkalosis was noted on the twenty-eighth hospital day, attributable possibly in part to the continued gastric aspiration. The urea clearance on the forty-fifth hospital day was 40% of average normal and the blood urea nitrogen 11.9 mg.%.

The fifth hospital admission occurred eight months later (4/15/37 to 4/20/37) because of a recurrent duodenal ulcer. Alkali had been taken infrequently prior to hospitalization. The

blood pressure at this time was 220/135. Forty-five grams of calcium carbonate and 150 gms. of sodium bicarbonate were given in five days. The urea clearance on the second day measured 37% and the blood urea nitrogen 32.0 mg.%; there was a slight chemical alkalosis at the time.

Five months later the patient was admitted for the sixth time (9/24/37 to 10/12/37). The urea clearance one week previously had measured 52% and the blood urea nitrogen 13.1 mg.%. The blood pressure was 180/100. Four hundred and twenty grams of calcium carbonate and 210 gms. of sodium bicarbonate were given in 19 days. Alkali therapy was complicated by a moderate chemical alkalosis which subsided after the administration of 4.0 gms. of ammonium chloride daily for five days. The urea clearance, after restoration of the acid-base balance, was 48% of average normal and the blood urea nitrogen 11.3 mg.%. Roentgen irradiation (a total of 3878 roentgen units) was directed to the fundus of the stomach through anterior and posterior portals for 14 days in an effort to reduce gastric acidity. A histamine achlorhydria was noted several weeks later (10/29/37). Alkali therapy was discontinued at this time and was not resumed thereafter.

Two admissions to the hospital were required during the next four years because of attacks of biliary colic which subsided without surgical intervention. The blood pressure varied from 140 to 218 systolic and from 90 to 128 diastolic. Urea clearances, seven and eight years after the initial visit, measured 70 and 67% of average normal respectively; the blood urea nitrogen values were 13.9 and 17.8 mg.%. The final clearance on June 19, 1941, eight years and three months after the original hospital entry, was 61% of average normal and the blood urea nitrogen 16.6 mg.%. No alkali had been taken for almost four years prior to this last determination.

Case 2.--I. J. S. (Unit no. 17834), a 31-year-old salesman, had experienced ulcer symptoms for one month prior to admission into the hospital. Physical examination was negative except for tenderness in the epigastrium; the blood pressure was 128/80. Roentgenograms revealed a stenosing duodenal ulcer. Three hundred and eighty-seven grams of calcium carbonate and 720 gms. of sodium bicarbonate were administered in 24 days (5/9/31 to 6/3/31). The urea clearance on the third day was 99% of average normal and the blood urea nitrogen 9.6 mg.%. A moderately severe alkalosis was

detected on the fifteenth hospital day. The urea clearance at this time was 78% and the blood urea nitrogen 10.9 mg.%. After recovery from the alkalosis, the patient was observed in the Out-Patient Department for six months; alkali was taken infrequently. The patient was then not seen by us for one year.

He re-entered the hospital on October 10, 1933, because of a massive hemorrhage. Physical examination disclosed the presence of a severe hypertension; the blood pressure varied from 180 to 200 systolic and from 100 to 114 diastolic. One hundred and fifty grams each of calcium carbonate and sodium bicarbonate were given in the first five days. A severe alkalosis was detected at this time and the alkali was discontinued. After restoration of the acid-base balance, the urea clearance increased from 41 to 63% and the blood urea nitrogen, which had risen to 28.4 mg.%, decreased to 13.8 mg.%. Six examinations of the urine were negative. Two months later the urea clearance measured 80% of average normal and the blood urea nitrogen 13.9 mg.%. Alkali was taken very infrequently in the subsequent five months. The hypertension persisted with readings in the neighborhood of 185/120.

Hospitalization again was necessary on March 19, 1934, because of sudden blurring of vision which had progressed to almost complete blindness. Physical examination revealed the presence of a definite hemi-analgesia; the blood pressure was 230/120. The patient developed involuntary movements and Jacksonian convulsions, and lapsed into a coma which persisted for several days. There was subsequently a rapid improvement both in mental clearness and vision. No alkali was administered during this period of hospitalization. Small quantities of a mixture of sodium citrate and tribasic calcium phosphate were taken daily during the next two and one-half years. The blood pressure fluctuated from 150 to 196 systolic and from 96 to 130 diastolic.

The patient entered the hospital a fourth time on May 24, 1937, because of recurrent bleeding. Four hundred and eighty grams of the sodium citrate, tribasic calcium phosphate mixture and 1020 gms. of the same combination of alkali with 10% ammonium chloride added were given in 25 days (5/24/37 to 6/18/37). The urea clearance on three occasions measured 23, 29, and 29% and the blood urea nitrogen varied from 19.5 to 26.0 mg.%. Roentgen irradiation (a total of 3050 roentgen units) was directed to the fundus of the stomach through anterior and posterior portals for

ten days in an effort to reduce gastric acidity. The irradiation produced a histamine achlorhydria which persisted for several months. During the subsequent 12 months the patient took no alkali. His blood pressure fluctuated from 146 to 156 systolic and from 80 to 98 diastolic. Occasional urines contained slight to moderate amounts of albumin. The specific gravity varied from 1010 to 1026. The final clearance on June 8, 1938, seven years after the initial determination, was 45% of average normal and the blood urea nitrogen was 28.6 mg.%.

It will be noted that both patients had received comparatively small quantities of alkali. Indeed, none had been taken for long intervals during the period of observation. In the first case the clearances of 67% and 61% actually represent good renal function in view of the hypertension and the numerous additional complications. In the second case, the appearance of hypertension two years after the initial visit is, we think, unrelated to the alkali therapy. The possibility that the alkali contributed to the impairment of renal function cannot be definitely excluded, but, in our opinion, the decreased urea clearances are attributable entirely to the hypertension and associated renal arteriosclerosis.

It seems clearly evident, therefore, that prolonged alkali therapy, even though complicated by alkalosis, does not permanently depress the urea clearance, regardless of the original status of renal function.

SUMMARY

Alkalosis, as indicated by electrolyte changes in the serum, occurred on 135 occasions in 111 patients with peptic ulcer treated by the Sippy program. Multiple episodes of alkalosis occurred in 18 patients. The disturbance was slight in 71 instances, moderate in 27, and severe in 37. The electrolyte balance was undisturbed during subsequent alkali therapy in 29 persons who had recovered from a previous alkalosis. The alkalosis was not a direct function of the quantity of alkali received. Symptoms usually appeared within four to ten days after the onset of treatment and consisted of a distaste for the milk and cream, weakness, dizziness, headache, dryness of the mouth, nausea and vomiting. Many patients with slight alkalosis and several with moderate or

severe alkalosis did not complain of any discomfort. There was no constant relationship between the severity of symptoms and the degree of chemical alkalosis.

Bleeding had occurred in 60 of the 135 episodes of alkalosis. There seemed to be no correlation between the severity of bleeding and the frequency of alkalosis. Gastric retention was present in 6 of 71 patients with slight alkalosis, in 10 of 27 patients with moderate alkalosis, and in 20 of 37 patients with severe alkalosis.

Genito-urinary disease was demonstrated in 16 patients. The urea clearance had been normal in three and reduced or low in six of this group. The acid-base balance was undisturbed in a group of 23 patients with renal disease similarly treated in whom renal function at the onset of treatment had been normal in ten and low in six. Thirty-seven of the 135 episodes of alkalosis occurred in patients with hypertension. The clearance previously had been normal in seven and low in 14 of this group. Alkalosis did not occur in a group of 17 hypertensive patients with ulcer similarly treated in whom renal function at the onset of treatment had been normal in seven and low in eight.

The effect of alkalosis upon the urea clearance was studied in 48 patients of the present series. Renal function at the onset of alkali therapy was normal in 24 and reduced or low in 24. The urea clearance during alkalosis did not change in 20 patients, in 14 of whom normal values had been obtained originally. Renal function diminished in 28 patients; it previously had been normal in 10 and low in 18 of this group. The depression of the urea clearance during alkalosis depended apparently upon two factors, (a) the severity of the alkalosis and (b) pre-existent impairment of renal function.

The urea clearance was determined within several weeks after alkalosis in 22 of the 28 patients in whom it had decreased during the acid-base disturbance. A return to the previous level was noted in 19 patients; the original value had been normal in 6 of these and low in 13. Failure to return to the previous level was observed in 3 patients; the original values had been normal in 2 of these and low in 1. The urea clearance later returned to its original level in all three patients.

The blood urea nitrogen was elevated during alkalosis in 55 instances. Hypertension was present in 16 patients of this

group, massive hemorrhage in 16, and gastric retention in 25. Albumin and casts were detected in the urine during alkalosis in 28 instances. Gross or microscopic hematuria was not observed.

It was not necessary to discontinue alkali or to administer additional chloride in 51 of the 135 patients. Treatment in the remaining cases consisted variously of a change of antacid, the administration of either ammonium or sodium chloride, with or without the discontinuance of alkali, and the use of parenteral fluids. Clinical improvement rather rapidly followed the institution of these therapeutic measures.

The effect of prolonged alkali therapy on renal function was studied in 62 patients in two groups: (a) those uncomplicated by alkalosis and (b) those in whom alkalosis developed. In (a) there were 29 patients. The urea clearance decreased in only one of this group, diminishing from 67 to 40% in a 68-year-old woman after the ingestion of large quantities of alkali for $5\frac{1}{2}$ years. The blood pressure, blood urea nitrogen, and the urine remained normal, however. In group (b) there were 33 patients among whom alkalosis occurred on 48 occasions. A decrease in the urea clearance was noted in only two patients of this group, each of whom had hypertension.

CONCLUSIONS

1. Alkalosis is a not infrequent complication of the Sippy treatment of peptic ulcer, although it may not be accompanied by clinical symptoms.

2. Alkalosis may develop in patients with normal renal function. The incidence of alkalosis is apparently greater in the presence of massive hemorrhage, the loss of gastric juice either by vomiting or therapeutic aspiration, and in the presence of pre-existing impairment of renal function.

3. The depression in renal function noted during alkalosis is usually temporary, although in occasional patients the decrease may persist for several months.

4. Renal function, as indicated by the urea clearance, is not permanently decreased by the prolonged administration of alkali.

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TABLE 1
ACID-BASE BALANCE DURING ALKALOSIS

Degree of Alkalosis	Number Patients	Avg. Age	Serum Chloride (mM/L)		Serum CO ₂ (mM/L)		Serum pH	
			Normal Range	95-105 Avg.	Normal Range	22-30 Avg.	Normal Range	7.35-7.45 Avg.
Mild	71	43	85.4-102.5	95.0	31 -39.8	34.1	7.40-7.65	7.51
Moderate	27	47	80.0- 91.1	88.0	35.9-43.3	39.2	7.50-7.72	7.56
Severe ..	37	51	60.0- 90.4	77.0	38.6-62.1	48.0	7.52-7.73	7.61
Totals	135							

TABLE 2
AGE INCIDENCE

Age (Decades)	Degree of Alkalosis		
	Mild	Moderate	Severe
20-29 ...	12	2	3
30-39 ...	16	5	8
40-49 ...	16	9	7
50-59 ...	17	6	6
60-69 ...	10	5	10
70-79 ...	..	.	3
Totals	71	27	37

TABLE 3
MULTIPLE EPISODES OF ALKALOSIS

Number Patients	Avg. Age	Episodes		Urea Clearance Prior to Alkalosis				Degree of Alkalosis		
		Two	Three	Normal	Slightly Reduced	Low	Undetermined	Mild	Moderate	Severe
18	43	13	5	5	3	6	4	22	7	13

TABLE 4
NORMAL ACID-BASE BALANCE DURING ALKALI THERAPY
AFTER ONE OR MORE EPISODES OF ALKALOSIS
(29 PATIENTS*)

Number Patients	Avg. Age	Episodes			Degree of Previous Alkalosis		
		After One	After Two	After Three	Mild	Moderate	Severe
29	40	24	4	1	13	7	9

*Limited to cases with available studies of acid-base balance during subsequent alkali therapy.

TABLE 5

OCCURRENCE OF ALKALOSIS IN PATIENTS WITH HEMORRHAGE FROM PEPTIC ULCER

Degree of Alkalosis	Number Patients	M	F	Average Age	Degree of Hemorrhage		
					Slight	Moderate	Severe
None	38	28	10	37 yrs.	3	9	26
Mild	34	30	4	44 "	7	9	18
Moderate	13	11	2	48 "	2	3	8
Severe ..	13	10	3	49 "	0	1	12
Totals	98	79	19				

22

TABLE 6

OCCURRENCE OF ALKALOSIS IN ULCER PATIENTS WITH RENAL DISEASE
(39 PATIENTS)

	Number Patients	Avg. Age	Renal or Ureteral Calculus	Other Renal Disease	Preceding Urea Clearance		Degree of Alkalosis		
					Normal	Low	Undetermined	Slight	Moderate Severe
Alkalosis ..	16	50	11	5	3	6	7	7	6 3
No alkalosis	23	42	21	2	10	6	7	.	None .

TABLE 7

OCCURRENCE OF ALKALOSIS IN ULCER
PATIENTS WITH HYPERTENSION
(54 PATIENTS)

	No. Pats.	Avg. Age	Preceding Urea Clearance			Degree of Alkalosis		
			Normal	Low	Undeter- mined	Mild	Moderate	Severe
Alkalosis ..	37	50	7	14	16	14	13	10
No alkalosis	17	53	7	8	2	..	..	..

TABLE 8

UREA CLEARANCE AT THE BEGINNING OF ALKALI THERAPY
(48 PATIENTS)

Degree of Alkalosis	Number Pats.	Urea Clearance at Onset of Alkali Therapy		
		Normal	Slightly Reduced	Low
Mild	23	12	3	8
Moderate	13	8	1	4
Severe ..	12	4	4	4
Totals	48	24	8	16

TABLE 9

UREA CLEARANCE DURING ALKALOSIS
(48 PATIENTS)

Degree of Alkalosis	Originally Normal (24 Pats.)		Originally Low (24 Pats.)	
	Unchanged in Alkalosis	Decreased in Alkalosis	Unchanged in Alkalosis	Decreased in Alkalosis
Mild	7	5	4	7
Moderate	7	1	2	3
Severe ..	0	4	.	8
Totals	14	10	6	18

TABLE 10

UREA CLEARANCE SHORTLY AFTER ALKALOSIS IN 22 PATIENTS IN WHOM A DECREASE
HAD BEEN OBSERVED DURING THE ACID-BASE DISTURBANCE

Subsequent Status	Number Patients	Original Urea Clearance		Degree of Alkalosis		
		Normal	Low	Mild	Moderate	Severe
Return to original level	19	6	13	9	2	8
Lower than original level	3	2	1	1	1	1
Totals	22	8	14	10	3	9

TABLE 11

DECREASED UREA CLEARANCE SHORTLY AFTER ALKALOSIS
(3 PATIENTS)

Patient Unit No.	Sex Age	Initial Urea Clearance		Days After Alk.	Clear- ance after Alk. % Avg. Normal	Blood Urea Nitrogen		Remarks	Subsequent Status of Urea Clearance
		% Avg. Normal	Mg. %			Mg. %	Mg. %		
W.M. 21508	M 36	84	10.1	7	48	14.7		Hypertension	Returned to original level
C.G.R. 35790	M 44	102	17.4	6	58	16.3		Nephrolithiasis Gastric retention	Returned to original level
C.M. 21508	M 54	32-37	20.8-26.3	10	15	35.0		Moderate hypertension	Returned to original level

TABLE 12

ELEVATED BLOOD UREA NITROGEN DURING ALKALOSIS

Blood Urea Nitrogen	Number Pats.	Associated Complications		
		Hemorrhage	Hypertension	Gastric Retention
A. Mild Alkalosis				
20- 30 mg. %	8	3	1	3
30- 40 "	2	1	1	.
40- 50 "	3	2	3	.
50-113.6 "	4	3	3	.
Totals	17	9	8	3
B. Moderate Alkalosis				
20-30 mg. %	8	1	2	3
30-40 "	3	1	1	2
40-52.5 "	2	1	.	.
Totals	13	3	3	5
C. Severe Alkalosis				
20-30 mg. %	7	1	2	4
30-40 "	8	2	2	5
40-50 "	7	1	1	5
59-75 "	3	.	.	3
Totals	25	4	5	17
GRAND TOTALS	55	16	16	25

TABLE 13

TREATMENT OF ALKALOSIS (135 PATIENTS)

Therapy	Degree of Alkalosis		
	Slight	Moderate	Severe
Alkali continued	46	5	0
Alkali stopped (no other treatment) ..	12	6	5
Change of alkali	5	1	0
Alkali contd. and NaCl or NH_4Cl added	5	5	2
Alkali stopped and NaCl or NH_4Cl added	1	6	18
Alkali stopped, parenteral fluids administered	2	4	12
Totals	71	27	37

TABLE 14
EFFECT OF PROLONGED ALKALI THERAPY WITH AND WITHOUT
ALKALOSIS ON THE UREA CLEARANCE (62 PATIENTS)

	Number Pats.	Avg. Age	Initial Urea Clearance			Status of Final Clearance		Amts. Alkali [†] Taken During Follow-up Period		
			Normal	Slightly Reduced	Low	Unimpaired	Lower than Original	Large	Moderate	Small
A. Therapy uncomplicated by alkalosis	29	44	18	7	4	28	1	17	9	3
B. Therapy complicated by alkalosis*	33	49	14	11	8	31	2	17	12	4
Totals	62		32	18	12	59	3	34	21	7

*48 episodes of alkalosis.

[†] Large quantities estimated as 40 to 60 gms. daily, moderate as 20 to 40 gms. daily, and small as 10 to 20 gms. daily.

PART II. THE ALKALOSIS OF SODIUM BICARBONATE

An Experimental Study

A. The Serum Electrolytes before and during
Acute Alkalosis in the Dog

B. Tolerance for Massive Doses. A Detailed Study
of the Acid-Base Balance and Urea
Clearance in One Patient

Section B accepted for publication in
Annals of Internal Medicine

INTRODUCTION

The clinical survey of alkalosis described in Part I indicated three possible causes for the electrolyte disturbance, namely, (1) ingestion of sodium bicarbonate, (2) ingestion of calcium carbonate, and (3) loss of chloride via gastric aspiration. To better understand the mechanisms involved in the alkalosis, an individual study of the effect of each of these factors upon the acid-base balance seemed desirable. The present section deals with the alkalosis induced by sodium bicarbonate and comprises (A) an investigation of the serum electrolytes before and during acute sodium bicarbonate alkalosis in the dog and (B) a study of the acid-base balance and urea clearance in a patient given massive doses of sodium bicarbonate.

A. THE SERUM ELECTROLYTES BEFORE AND DURING ACUTE ALKALOSIS IN THE DOG

METHOD OF STUDY

Alkalosis was produced in a 19 kg. dog by the intravenous injection of varying quantities of sodium bicarbonate in distilled water at seven-day intervals for a period of five weeks. In an additional experiment, a mixture of sodium chloride and sodium bicarbonate was administered to determine the effect of the added chloride on the degree of the alkalosis. Venous blood was withdrawn under oil from the jugular vein before each experiment and at intervals of 5 to 35 minutes after the injection of alkali (see Table 1) and utilized for the following determinations: serum carbon dioxide, pH, and chloride (1), calcium (2), phosphorus (3), sodium (4), and total base (5). Measurements were made also of the cell volume and serum water (6). The carbon dioxide tension and the bicarbonate content of the blood were calculated from the CO_2 and pH values using the Henderson-Hasselbach equation.¹ The concentration of electrolytes was calculated also

$$^1 \text{pH} = \text{pK}' + \log \frac{[\text{B} \cdot \text{HCO}_3]}{[\text{H} \cdot \text{HCO}_3]}$$

as milli-equivalents per kilo of serum water (osmolar concentration), but since no significant additional information was obtained thereby, these data are omitted.

RESULTS

Clinical manifestations during alkalosis consisted of restlessness, retching, and rapid, shallow respirations. In addition, the dog during Experiment V became extremely weak and momentarily exhibited convulsive movements. These symptoms subsided rapidly, however, and the animal appeared in good condition several hours after the discontinuation of alkali. The onset of clinical improvement coincided usually with the appearance of a marked diuresis. The pH of the urine at this time ranged from 7.6 to 7.95. Tetany was not observed at any time.

The results as shown in Table 1 and Figure 1 indicate the unusual severity of the alkalosis induced in these experiments. The most striking changes in the electrolyte structure consisted of a marked increase in total base, due exclusively to the rise in sodium and a similar elevation of the bicarbonate content of the blood. There was a slight decrease in the serum chloride and calcium and a more definite lowering of the serum phosphorus. These latter changes are probably attributable to dilution of the blood caused both by the injection of fluid and by the hypertonicity of the sodium bicarbonate solution. The absence of tetany in this dog is probably explained by the fact that the carbon dioxide tension of the blood was not diminished. Shock and Hastings (7) have demonstrated that tetany appears only when the carbon dioxide tension of the blood falls below the critical level of 20 mm. of mercury. The results of Experiment VI clearly show that added sodium chloride did not prevent or diminish the severity of the alkalosis induced by sodium bicarbonate. Indeed, the sodium and total base values were higher than those obtained with comparable amounts of alkali alone; this finding is, of course, to be expected in view of the increased total quantity of sodium ion injected.

CONCLUSION

A severe alkalosis can readily be induced in the dog by

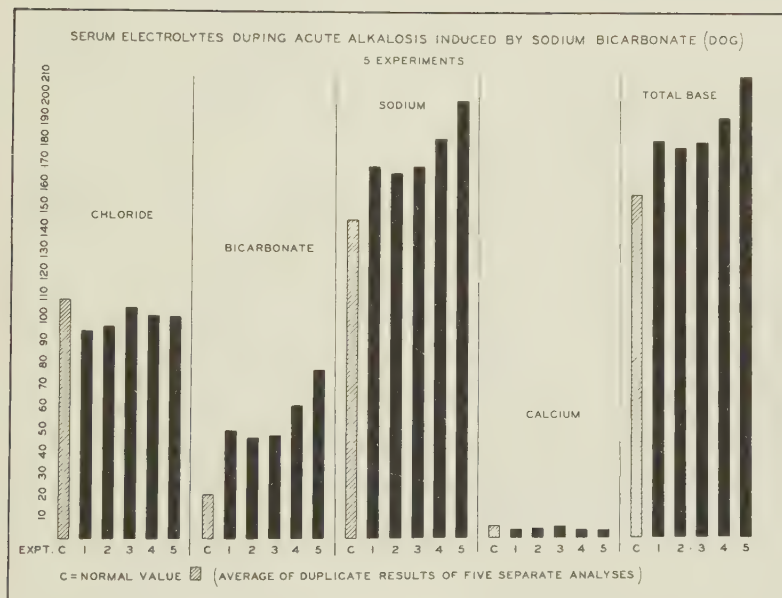


Fig. 1.--Serum electrolytes during acute alkalosis induced by sodium bicarbonate (dog).

the intravenous administration of sodium bicarbonate. The acid-base disturbance is characterized by a marked elevation of the sodium and total base and by a similar increase in the bicarbonate content of the blood. The serum chloride, calcium, and phosphorus diminish slightly, probably as a result of the accompanying hydemia.

B. TOLERANCE FOR MASSIVE DOSES. A DETAILED STUDY
OF THE ACID-BASE BALANCE AND UREA
CLEARANCE IN ONE PATIENT

INTRODUCTION

It has been shown in Part I that antacid therapy may be continued for years without significant alteration in the acid-base balance or in renal function. This tolerance to alkali is illustrated to an unusual degree in the following case in which the ingestion of 32,000 gms. of sodium bicarbonate in 20 months produced only slight changes in the serum electrolytes and no demonstrable decrease in the urea clearance.

Case E. L. R., a 23-year-old unemployed shipping clerk, had experienced ulcer distress for five years, during which time hospitalization had been required on two occasions because of massive hemorrhage. Alkalosis was said to have been present on one occasion as a result of the excessive ingestion of alkali following the appearance of tarry stools. This occurred one year before his admission to the University Clinics. Physical examination at the time of admission was negative except for localized tenderness in the epigastrium. Roentgen studies disclosed a stenosing duodenal ulcer with a crater measuring 15 mm. in diameter. The patient was observed in the hospital for 11 months (September 3, 1938, to August 1, 1939) and subsequently in the University Clinics until November 13, 1940, a total period of 27 months.

METHOD OF STUDY

No alkali was administered for several days. Control determinations were made of the serum CO_2 , pH and chloride, and of the blood urea nitrogen (8). Renal function was estimated by several urine concentration tests and by the urea clearance test (9). These studies were repeated at least twice each week during the period of hospitalization and at less frequent intervals in the Out-Patient Department. Occasional measurements were made also of the total base in the blood.

Diet: Protein Intake

The basic diet in the hospital consisted of a mixture of

90 cc. of equal parts of milk and cream taken at hourly intervals from 7 A. M. to 7 P. M. Feedings consisting of soft bland foods were added gradually so that after four weeks the patient received a modified three-meal ulcer diet with milk and cream at hourly intervals. After discharge from the hospital, the quantity of milk and cream was decreased and the three-meal program enlarged. The protein intake, though somewhat reduced during the initial four weeks, was consistently above basal requirements, averaging 55 gms. daily for the first month (September 3 to 30, 1938), 77 gms. during the second month (October 1 to 31, 1938), and 102 gms. daily between November 1 and 30, 1938. The protein intake during December (December 1 to 31, 1938) averaged 88 gms. per day and was maintained at approximately this level for the remainder of the study.

Fluid Balance

The fluid intake and output were measured daily between November, 1938, and August, 1939, and are recorded as averages per day during each month in Table 2. The large quantities of alkali administered precluded occasional efforts to reduce the 24-hour fluid intake below 3000 cc. The gastric contents were aspirated nightly for a period of six months (November, 1938, to April, 1939). The quantities removed varied widely, ranging from 30 to 950 cc.; the average daily amounts withdrawn are noted in Table 2. It will be observed that the volume of aspirate per day gradually decreased from an average of 388 cc. in November, 1938, to 143 cc. in April, 1939.

Alkali Therapy

This was begun several days after admission to the hospital and was continued for 20 months; the intake per month is shown in Figure 2. Between September 6, 1938, and September 30, 1938, the patient received 135 gms. of sodium bicarbonate, 219 gms. of calcium carbonate, and 352 cc. of aluminum hydroxide. During October, 1938, 48 cc. of aluminum hydroxide, 302 gms. of calcium carbonate, and 830 gms. of sodium bicarbonate were administered. The daily intake averaged 90 gms. for the eight-month period between November 1, 1938, and August 1, 1939. The quantity of alkali was then gradually reduced to 60 gms. daily be-

tween August 1, 1939, and December 1, 1939; the alkali intake for the five-month period between December 1, 1939, and April 22, 1940, averaged 30 gms. per day. The total amount of alkali administered during the 20 months between September 6, 1938, and April 22, 1940, consisted of 400 cc. of aluminum hydroxide, 881 gms. of calcium carbonate, and 31,414 gms. of sodium bicarbonate. Alkali was taken only occasionally during the final seven months (April 23, 1940, to November 13, 1940), and the intake was comparatively small.

RESULTS

Routine Laboratory Data and Clinical Course

The red and white blood cell counts and the hemoglobin remained within normal limits. Three histamine tests (0.6, 0.6, 0.65 mg.) disclosed a maximum free acidity of 118, 110, and 150 clinical units respectively. Forty-five urine specimens were examined; the specific gravity varied from 1015 to 1034, averaging 1024; the reaction was constantly alkaline; a trace of albumin was detected on four occasions. Numerous electrocardiograms revealed no significant changes during alkali therapy. The patient's clinical course was entirely uneventful. His body weight gradually increased from 54 kg. to 66 kg. during the 27-month period of observation. The ulcer crater disappeared in five weeks and did not reappear.

Acid-Base Balance

The acid-base balance was determined 78 times during the study (Fig. 2). The serum CO_2 during the period of hospitalization varied usually from 31 to 35 mM/L with increases to 37.7 and 39.2 mM/L on two occasions. After discharge from the hospital (August 1, 1939, to November 13, 1940) the CO_2 remained within normal limits. The serum pH paralleled the CO_2 and fluctuated usually from 7.33 to 7.50, although values between 7.50 and 7.53 were noted. The total base was determined on 18 occasions; only two of the results (163.4 and 164.9) exceeded the normal range of 150 to 160 milliequivalents per liter. The serum chloride was consistently within the normal limits of 95 to 105 millimols per liter.

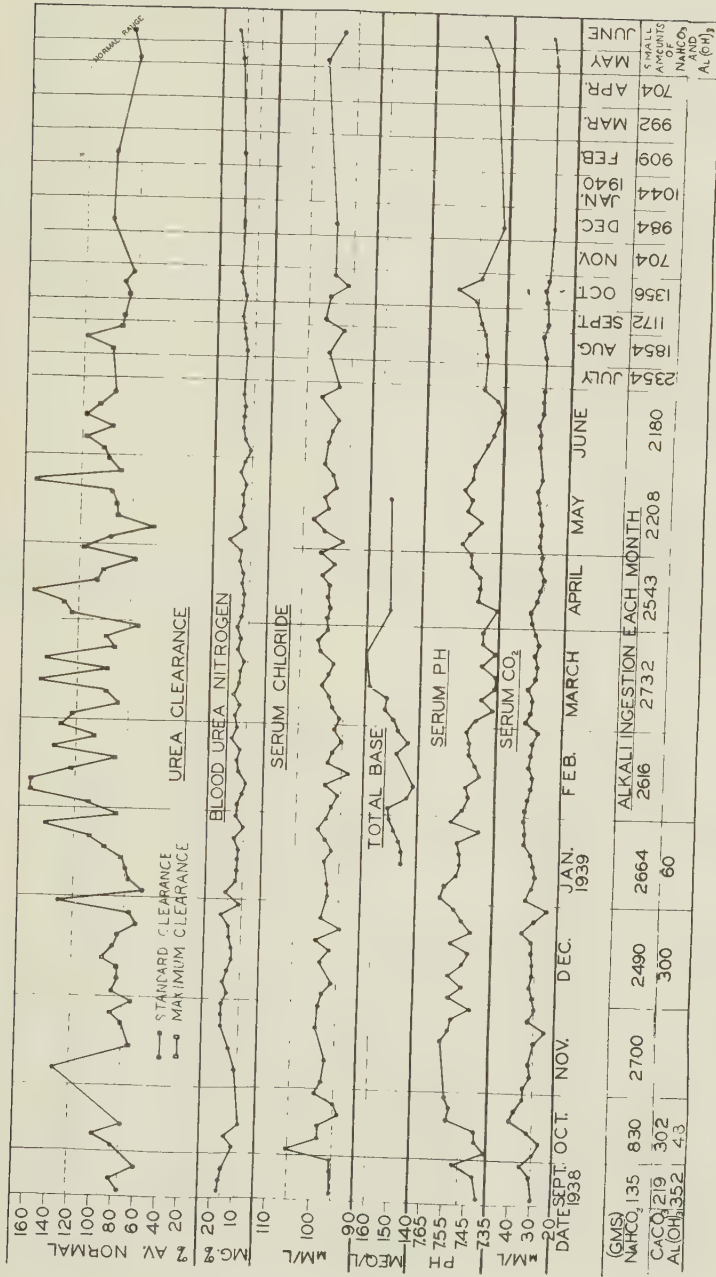


Fig. 2.--Acid-base balance and urea clearance during ingestion of massive amounts of sodium bicarbonate.

Renal Function

Two urine concentration tests before alkali therapy revealed maximum specific gravities of 1025 and 1027. Three urea clearance tests during the control period measured 60, 75, and 80% of average normal respectively (lower limit of normal considered to be 75%). The urea clearance subsequently was determined on 75 occasions in the succeeding 27 months; 30 of these were by the standard clearance with urine volumes between 1 and 2 cc. per minute. Forty-five of the determinations were by the maximum clearance; the urine volumes varied from 2.1 to 9.2 cc. per minute. The urea clearance was below 75% on ten occasions; the other 65 clearances fluctuated within the normal range of 75 to 150%. It is of interest to note that the two final clearances of 75 and 80%, after the administration of 32,000 gms. of alkali, duplicated the values obtained before alkali therapy.

Blood Urea Nitrogen

The blood urea nitrogen remained normal throughout the entire study. The values ranged from 8.2 to 16.5 mg.% with an average of 11 to 12 mg.%.

COMMENT

It will be noted that despite the continued ingestion of massive amounts of sodium bicarbonate, the serum electrolytes were altered only slightly in this patient. These changes consisted of a mild increase in the serum CO_2 and pH. No significant diminution of the serum chloride was observed. Previous studies (10) have shown that the administration of sodium bicarbonate results in an elevation of the bicarbonate content and pH of the blood. In normal subjects the maximum increase in bicarbonate and pH occurs 1 to 1½ hours after the ingestion of alkali (7). Bicarbonate is eliminated rapidly during the succeeding 1 to 1½ hours, the values decreasing to about 50% of the maximum level. The remainder of the alkali is excreted rather slowly, complete recovery sometimes not occurring until the following day. Palmer and Van Slyke (11) found that following the use of sodium bicarbonate, the plasma bicarbonate of patients with nephritis often rose considerably higher than the level seen in normal in-

dividuals before the urine became alkaline. Ellis (12) observed a definite bicarbonate excess and a high serum pH in a nephritic patient with acid urine; others (13) have reported similar findings.

Persistent alkalosis following the ingestion of sodium bicarbonate represents, therefore, a retarded excretion of this alkali. The remarkable tolerance to sodium bicarbonate exhibited by this patient is attributable presumably to the excellent renal function and reserve capacity of the kidney, as well as to the large volume of fluid available for the excretion of the alkali. Apparently the normal kidney can cope successfully with excesses of alkali for a prolonged time without untoward effects, provided adequate amounts of water are available.

CONCLUSION

The administration of 32,000 gms. of sodium bicarbonate in 20 months to a patient with normal renal function produced no marked alterations in the acid-base balance and no decrease in the urea clearance.

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TABLE 1

THE CONCENTRATION OF ELECTROLYTES AND WATER IN THE SERUM OF THE DOG BEFORE
AND DURING ACUTE ALKALOSIS INDUCED BY SODIUM BICARBONATE

No. of Experi- ment	Amt. NaHCO ₃ (gm.)	Amt. Distilled Water (cc.)	Injection		Serum Water		Cell Volume %
			Duration of	Time of Analysis	gm./L	gm. %	
Control I	27.4	364	60 min.	30 min.	929.9 935.0	91.85 92.11	49.5 41.5
Control II	28.1	375	48 min.	35 min.	931.5 940.0	91.90 92.15	46.2 40.0
Control III	28.5	285	47 min.	30 min.	935.8 932.8	92.06 91.58	47.3 45.0
Control IV	41.3	330	47 min.	20 min.	936.2 931.2	91.55 91.90	42.5 39.5
Control V	42.5	340	30 min.	5 min.	922.4 947.9	91.67 93.18	43.0 45.0
Control VI	23.5*	282	30 min.	12 min.	924.2 943.8	91.69 92.28	46.0 38.5

*Plus 16.5 gm. NaCl.

TABLE 1--Continued

No. of Experi- ment	pH	pCO ₂	CO ₂		BHCO ₃	Cl	Na	Ca	Total Base	P
		mmHg	(mM/L)		(mEq./L)					
Control I	7.42	31.4	20.7	19.76	104.0	148.8	5.55	159.4	1.13	
	7.83	30.5	50.1	49.18	94.4	169.0	4.55	181.0	0.61	
Control II	7.40	33.2	21.3	20.3	104.0	142.7	5.05	154.7	1.20	
	7.81	30.03	47.2	46.3	97.0	166.4	4.85	178.3	0.70	
Control III	7.39	33.8	21.0	19.98	110.8	144.6	5.45	156.6	1.55	
	7.60	49.5	48.8	47.31	105.0	169.3	5.10	180.2	0.54	
Control IV	7.40	33.5	21.7	20.69	107.2	143.9	5.50	155.0	1.30	
	7.84	36.9	62.0	60.89	101.8	182.5	4.55	192.1	0.45	
Control V	7.41	31.6	22.7	21.75	110.8	143.8	5.40	160.4	0.97	
	7.93	37.5	77.8	76.67	100.8	199.0	4.10	209.7	0.76	
Control VI	7.42	35.2	23.2	22.24	112.0	147.6	4.88	158.4	0.903	
	7.76	31.0	43.5	42.57	134.8	194.3	4.50	202.3	0.610	

TABLE 2
FLUID BALANCE

Month Year	Average Daily Fluid Intake (cc.)	Average Daily Urinary Output (cc.)	Aspiration	
			Average Daily Amount (cc.)	Number of Days Aspirated
Nov., 1938	3478	2458	388	10
Dec., 1938	3253	2539	347	27
Jan., 1939	3718	2923	282	22
Feb., 1939	5011	3936	228	28
Mar., 1939	4951	3378	188	29
Apr., 1939	4588	3377	143	25
May, 1939	4326	2650	...	..
June, 1939	4422	2780	...	..
July, 1939	3446	1792	...	..

PART III. THE ALKALOSIS OF CALCIUM CARBONATE

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INTRODUCTION

In Part II it was suggested that the ingestion of calcium carbonate might contribute to the development of alkalosis, although this antacid was originally considered to have no significant effect either on the acid-base balance or on mineral metabolism (1). A recent paper by McGee *et al.* (2) supports the view that moderate amounts of calcium carbonate do not alter the serum electrolytes. In contrast to these studies are the reports of Wildman (3), Gatewood (4), Cooke (5), and Cope (6) describing the occurrence of alkalosis in patients receiving only calcium carbonate. A study, accordingly, was made of the effect of this alkali on the acid-base balance and on renal function in a group of patients with peptic ulcer.

METHOD OF STUDY

One hundred and five patients with peptic ulcer, including both sexes, and of ages from 16 to 78, were placed on regular Sippy management with the exception that calcium carbonate, in doses averaging 30 gms. daily, was administered instead of the usual sodium bicarbonate-calcium carbonate mixture. The serum CO_2 , pH, and chloride, and the blood urea nitrogen (7) were determined at different periods during treatment, the number of such determinations varying with the individual case. In addition to the routine urine examinations, renal function was estimated by the urea clearance method of Van Slyke (8). These values are expressed as per cent of average normal after correction for individual surface area by the method of Peters and Van Slyke. Seventy-five per cent is generally accepted as the lower limit of normal. Although a normal urea clearance does not exclude the possible presence of renal disease (9), it is, nevertheless, one of the most reliable measures of renal function in use today (10).

RESULTS

Occurrence of Alkalosis and Clinical Manifestations

Alkalosis, as evidenced by an alteration of the acid-base balance, developed in 32 of the 105 patients (see Table 1). The alkalosis was arbitrarily classified as mild to moderate in 12 and severe in 20. There was no direct correlation between the amount of calcium carbonate received and the development of alkalosis. The daily intake of alkali varied from 15 to 60 gms., averaging 30 gms. in the "alkalosis" group, and varied from 15 to 60 gms., averaging 32 gms. in the normal group. Symptoms usually appeared between the third and eighth days of treatment although, in several instances, not until after fourteen to eighteen days. The significant complaints were a distaste for the milk and cream, anorexia, dizziness, headache, weakness, nausea, and occasionally vomiting. Tetany, convulsions, and coma were notably absent. Symptoms did not occur in several patients despite the presence of a severe chemical alkalosis. There was no consistent correlation between the severity of complaints and the degree of chemical alkalosis.

Changes in Serum Electrolytes

The characteristic changes noted in the blood serum were an elevation of the CO_2 and pH, and a lowering of the chloride (Table 1). Thus, in the twelve individuals with mild to moderate alkalosis, the carbon-dioxide varied between 31.7 and 37.0 mM/L; in the twenty patients with severe alkalosis the values were higher, exceeding 40 mM/L in ten cases. In one instance the CO_2 reached a peak of 47.4 mM/L. The serum pH paralleled the CO_2 , although temporary values of about 7.50 were occasionally observed in patients with an otherwise normal electrolyte balance. The pH during alkalosis varied between 7.50 and 7.73, exceeding 7.60 in eleven patients. In general, the chloride curves were mirror images of the CO_2 and pH curves. In mild to moderate alkalosis the lowest chloride values varied between 81.0 and 96.4 mM/L and in five cases were below 90 mM/L. In severe alkalosis the lowest chloride values varied between 65.8 and 89.4 mM/L. In all these cases the serum chloride was below 90 and in five patients the values were below 80 mM/L.

The total base (11) was determined in twenty patients, twelve with a normal acid-base balance, and eight with alkalosis. Contrary to the observations of Cope, the values did not exceed the normal range of 150 to 160 milliequivalents per liter, and there was no significant variation in the total base of patients with and without alkalosis (see Fig. 1). Keifer, among others, has also noted the occurrence of alkalosis without an appreciable rise in total base.

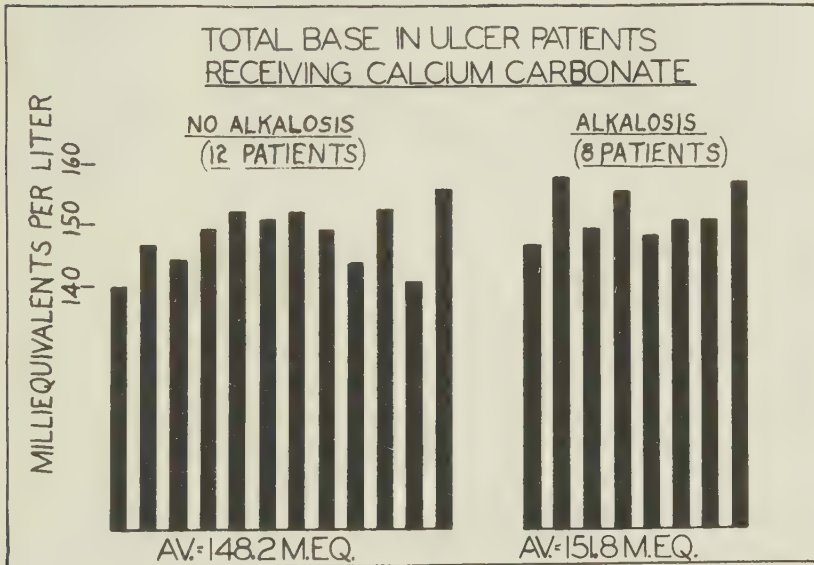


Fig. 1

The serum calcium and phosphorus were determined in twenty-three patients with a normal electrolyte balance and in five patients with alkalosis (Figs. 2 and 3). All values were normal except in one patient with pyloric stenosis in whom a serum calcium of 13.1 mg.% was obtained.

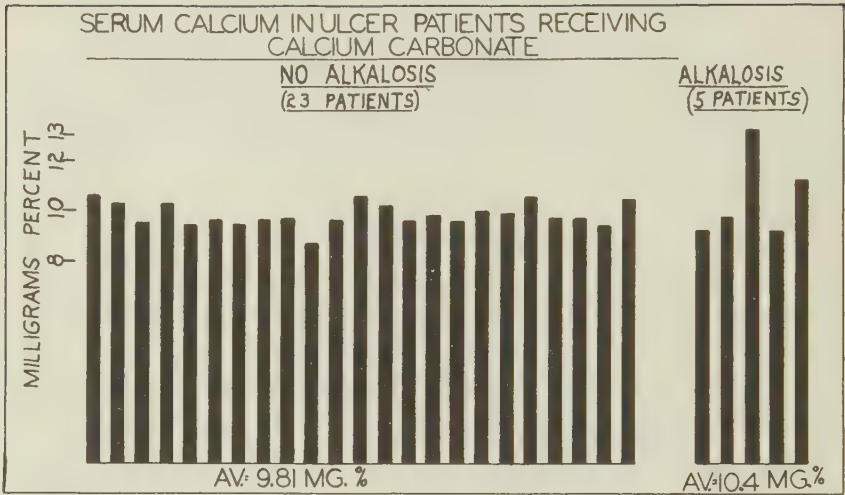


Fig. 2

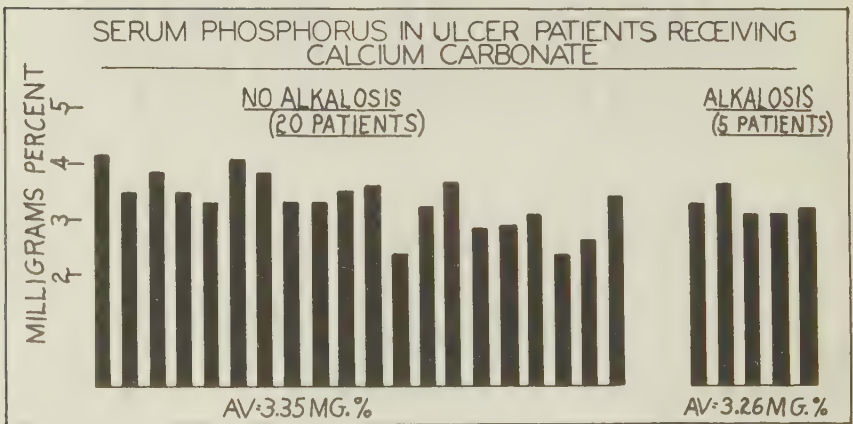


Fig. 3

Renal Function

(a) Prior to therapy.--Normal renal function, as indicated by the urea clearance, was present in 22 of 32 cases in the present series, prior to the development of alkalosis. Twelve patients with lowered renal function showed no disturbance in the acid-base balance during treatment. It is interesting to note the absence of alkalosis in three patients with hypertension and in one individual who had undergone a nephrectomy 20 years previously.

(b) During alkalosis.--During alkalosis the urine in the present series, in contrast to the observations of some writers (12), rarely contained albumin, casts, and red blood cells. Albumin was present in the urine of two patients. In a third case, an acid urine containing albumin, casts, and red blood cells was secreted at the height of the alkalosis. This was the only instance of an acid urine during alkalosis, although it has been reported frequently by others. The blood urea nitrogen frequently rose to very high levels and fell with recovery (13).

In the present series, the urea clearance during alkalosis decreased in 25 of the 32 patients (see Table 3). In nine cases the urea clearance dropped to levels as low as 12, 13, 15, 17, 17, 17, 18.5, 20, and 22% of average normal. The blood urea nitrogen rose concomitantly, reaching a peak of 67.6 mg.% in one patient. The urea clearance remained unchanged in seven patients, although in three the alkalosis was severe. Normal clearances had been obtained previously in five of this group.

The urea clearance decreased during calcium carbonate therapy in eight patients without alkalosis. In four, the clearance previously had been either low or at the lower limit of normal. However, the drop in values varied from 10 to 15% and was of no clinical significance.

(c) After alkalosis.--Few studies have been reported in the literature on the status of renal function after the subsidence of alkalosis. The evidence available (14) indicates that the kidneys usually recover completely their original function within several weeks or two to three months. Jeghers and Lerner (12), Steele (15), and Berger (16) have noted that, in occasional patients, the lowered renal function may persist for some time. In the present series, renal function returned to its original

level in 24 of the 25 patients after subsidence of the alkalosis (see Table 4).¹ This improvement was noted usually within seven to fourteen days after the onset of treatment. In some patients recovery occurred within two or three days, while in four cases, one, three, six, and eight months elapsed before recovery was complete.

COMMENT

The mechanism of the alkalosis described in this series of patients is not entirely clear, although it is probable that more than one factor is involved. As noted previously, antecedent renal damage was not present in the majority of cases. It has been suggested (17) that part of the carbonate ion may be absorbed into the blood as bicarbonate, thereby disturbing the acid-base balance. Although the total base values did not exceed normal limits, this possibility must be considered seriously. Cooke has suggested also that insoluble salts may "fix" the gastric acid, thus preventing the normal neutralization of a portion of the alkaline intestinal secretions and making available for absorption an increased quantity of base.

The hypochloremia associated with the alkalosis is undoubtedly an important etiologic factor. The daily intake of sodium chloride on the Sippy regimen given these patients was low. It was estimated to vary between 1.5 and 2.3 gms. as compared with the average normal intake of 8 to 12 gms. Chloride loss may result from the aspiration of gastric contents, one of the routine procedures in the Sippy program. Marked depletion of chloride occurs also after persistent vomiting. Consequently, from 0.5 to 2.0 gms. of chloride ion may be removed or lost daily from a patient already on a low chloride intake. The loss of chloride by this method is considerably greater in patients with gastric retention and pyloric stenosis. The quantity of gastric contents removed in the group with alkalosis exceeded 200 cc. in 19 patients. In 12 of the remaining 13 cases, the average daily volume of gastric aspiration ranged from 110 to 195 cc. A history of vomiting prior to hospitalization was recorded in eight of

¹Unilateral nephrolithiasis and suppurative nephritis (onset long before alkali therapy) were present in the one patient with a persistently lowered urea clearance.

these individuals, while vomiting had occurred after a radical mastectomy in the one patient who was not aspirated. Thus, there was some evidence of chloride loss in the entire group with alkalosis. It is of interest to note that the acid-base balance remained normal during calcium carbonate therapy in five patients whose aspirations exceeded 200 cc. daily.

Kiefer (18) has attributed the increased frequency of alkalosis when gastric hypersecretion is present, to the loss of chloride resulting from increased sodium excretion. Another possibility is that calcium carbonate may remove chloride from the gastric juice, some of which may not be reabsorbed. Binger and Goldschmidt (19) have shown that calcium lactate in increasing concentration first accelerates, then inhibits the absorption of chlorides from solutions of sodium chloride in the bowel. The question of intestinal absorption of chloride is obviously a complicated problem since, as Lyall (20) points out, intestinal secretions contain up to 0.64% sodium chloride while the chloride concentration of the intestinal contents for absorption is of the same order. The problem may be related to differences in gastric secretion, variations in the salt intake and salt reserve of the body, and varying plasma volumes prior to treatment. In this connection, one patient with alkalosis had worked near blast furnaces and, although he perspired profusely, did not take the sodium chloride tablets which were available.

The decreased urea clearances observed during alkalosis in the present series are of considerable interest. It has been recognized for some time that lowered renal function is a regular concomitant of hypochloremia. Romalo and Dumitresco (21) observed in 1914 that the blood urea nitrogen was higher in nephritis during periods of reduced salt intake than in periods when the diet contained more salt. Chabanier (22), Host (23), and Landis et al. (24) have also noted a decrease in renal function during periods of reduced salt intake. These observations were not confirmed by Cope (25) who apparently produced only a mild chloride deficiency. Many investigators, especially the French (26) believe that the decrease in chloride impairs renal function and is directly responsible for the acute rise in non-protein nitrogen. This theory has been disputed by Kerpel-Fronius (27), Clausen (28), and others (29) who attribute the so-called "azotemia" to a withdrawal of sodium and its sequelae.

The normal volume of extra-cellular fluid cannot be maintained without normal amounts of sodium and chloride; consequently, the loss of these ions is invariably accompanied by a decrease in the extra-cellular fluid, or dehydration (30). McCance (31) has actually found a reduction of 28 to 38% in the volume of body fluids in experimental human salt deficiency. It is likely, therefore, that dehydration may have been present in these patients. Indeed, dehydration may occur even though the total body water remains unchanged, for the intracellular content of fluid may be increased at the expense of the extracellular fluid (32). Renal function is usually decreased in dehydration. McCance and Widdowson have observed a fall in the creatinine, sucrose, inulin (9), and urea clearances in experimental salt deficiency. The lowered renal function has been attributed to a reduction in the rate of glomerular filtration which may itself result from a combination of factors. These include increased colloidal osmotic pressure of the blood, decreased blood volume, increased blood viscosity, a reduction in the number of "active" glomeruli (due to the decreased blood volume), and a decreased rate of circulation (33). In fact, Gømbri and his co-workers (34) have demonstrated a reduction in the rate of circulation and a decrease in filtration pressure under similar conditions. The lowered urea clearances described in the present study suggest that the temporary impairment of renal function was due either to a decreased renal blood flow, or to a less complete extraction of urea from the blood. Since the renal tubules function best when the serum electrolytes are normal (35), it is possible, also, that decreased tubular efficiency may be responsible, in part, for some of the changes. The elevated blood urea nitrogen does not necessarily indicate renal failure in the pathological sense (36); it is due to the decreased renal function and perhaps to increased tissue catabolism associated with the dehydration (37).

CONCLUSIONS

1. Alkalosis, as evidenced by an alteration in the acid-base balance of the blood, occurred in 32 of 105 patients receiving calcium carbonate during the Sippy treatment of peptic ulcer.

2. Whether the alkalosis can be attributed, even in part, to the administration of calcium carbonate is, perhaps, not com-

pletely established because all of these patients vomited or were being aspirated. The changes were not due to an increase in the serum calcium or total base because these values remained normal. The serum chloride was lowered and this reduction of chloride may be responsible for the entire syndrome. The diminution in the serum chloride was due mainly to the loss of chloride per se without adequate chloride replacement. The possibility of some of the chloride being carried off in the feces with the unabsorbed calcium has not been excluded.

3. The urea clearance was normal in 22 of the 32 patients prior to the development of alkalosis.

4. The urea clearance decreased during alkalosis in 25 of the 32 patients. Renal function returned to its original level in 24 of these 25 individuals after correction of the acid-base balance.

5. The changes in the urea clearance were similar to those encountered during hypochloremia and dehydration.

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TABLE 1

ACID-BASE BALANCE DURING ADMINISTRATION
OF CALCIUM CARBONATE
(105 PATIENTS)

	Serum CO ₂ (mM/L) ²	Serum pH	Serum Cl (mM/L)
No alkalosis (73 patients)	22-30	7.35-7.45 occasionally 7.50	95-105
Mild to moderate alkalosis (12 patients)	31.7-37.0	7.50-7.60	81.0-96.4
Severe alkalosis (20 patients)	35.0-47.4	7.50-7.73	65.8-89.4

TABLE 2

UREA CLEARANCE PRIOR TO ADMINISTRATION
OF CALCIUM CARBONATE

	Group I Patients not Developing Alkalosis	Group II Patients Developing Alkalosis
Normal urea clearance ...	61 (83.6%)	22 (68.7%)
Lowered urea clearance ..	12 (16.4%)	10 (31.3%)
Totals	73	32

TABLE 3

UREA CLEARANCE DURING ADMINISTRATION
OF CALCIUM CARBONATE

	Group I No Alkalosis	Group II Alkalosis
Urea clearance unchanged ...	65	7
Urea clearance decreased ...	8	25
Totals	73	32

TABLE 4

UREA CLEARANCE AFTER SUBSIDENCE OF
ALKALOSIS (27 PATIENTS)

Normal clearance at all times	2
Persistent lowering of clearance	1
Return to original clearance	24
Return to normal acid-base balance	27

PART IV. THE THERAPEUTIC AND PROPHYLACTIC VALUE OF SODIUM
CHLORIDE IN THE ALKALOSIS OF CALCIUM CARBONATE

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A. THE THERAPEUTIC VALUE OF SODIUM CHLORIDE

INTRODUCTION

Hartwell and Hoguet (1) apparently were the first to use sodium chloride in the treatment of the alkalosis of experimental intestinal obstruction. The specific effect of salt in relieving the metabolic disturbance in pyloric and high intestinal obstruction was subsequently established in numerous experimental and clinical studies (2). The use of sodium chloride in the treatment of alkalosis complicating alkali therapy likewise has been found highly effective, although the discontinuance of alkali undoubtedly has played a major role in the recovery of these patients. Wildman (3) and Gatewood (4), in fact, attributed a large proportion of the symptoms of alkalosis to the associated hypochloremia. It has been recognized for some time that the clinical and chemical manifestations of experimental human salt deficiency closely resemble those of alkalosis arising during alkali therapy (5). The evidence presented in preceding sections indicated, furthermore, that of the two mechanisms chiefly involved in the alkalosis complicating the Sippy treatment, namely ingestion of alkali and chloride loss, depletion of chloride apparently was the more important.

METHOD OF STUDY

In view of these considerations, it seemed important to determine whether or not the addition of sodium chloride could suffice to correct the acid-base balance despite the continuation of alkali. The first opportunity to test this possibility arose in the following case:

Case 1.--R. F. (Unit no. 211953) (Fig. 1), a 24-year-old travel agent, entered the hospital following a severe massive hemorrhage from a duodenal ulcer. On the seventh day of calcium carbonate therapy, acid-base studies revealed a mild alkalosis which became severe four days later. Sodium chloride was added to the program on the twelfth day. Despite the continuation of

calcium carbonate, the acid-base balance gradually improved and returned to normal after 14 days of sodium chloride therapy. The blood urea nitrogen dropped from a peak of 54.7 mg.% and the urea clearance rose from 13 to 61% of average normal. The patient showed no further signs of alkalosis despite continued calcium carbonate therapy for a period of two years. The urea clearance was then 85% and the blood urea nitrogen 15.3 mg.%.

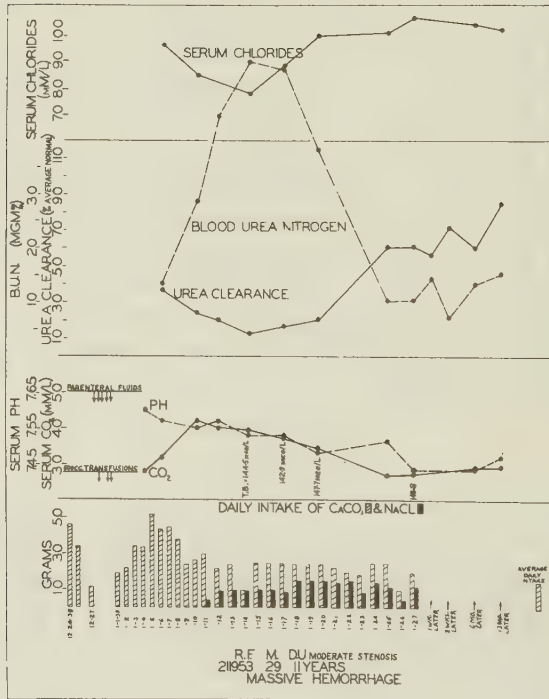


Fig. 1.--Effect of added sodium chloride on acid-base balance and urea clearance during continued calcium carbonate therapy in Case 1.

The following case demonstrates further that, even in severe alkalosis, the addition of sodium chloride to the program may correct the acid-base disturbance despite the continued use of calcium carbonate.

Case 2.--M. W. (Unit no. 31868) (Fig. 2), a 68-year-old housewife, had complained of ulcer symptoms for 11 years. She had been treated at the University Clinics for nine years during which time alkalis had been taken periodically. Her blood pressure fluctuated between 198 and 210 systolic and 100 diastolic, but renal function (urea clearance and concentration tests) was normal. Prior to entry into the hospital the patient had vomited repeatedly. Roentgenograms revealed a marked pyloric stenosis. Severe alkalosis was noted on the fifth day of therapy. The urine contained occasional hyaline casts; its specific gravity was 1026. Sodium chloride was added to the program on the sixth day, the alkali being continued. The acid-base balance and renal function returned to normal after ten days of sodium chloride treatment. In the following year the patient showed no evidence of alkalosis despite the continued use of calcium carbonate.

RESULTS

An additional 25 patients with alkalosis during the administration of calcium carbonate were treated similarly. The quantity of sodium chloride prescribed varied from 3.0 to 15.0 gms. daily. Clinical improvement promptly occurred in all 27 cases. The acid-base balance returned to normal within three to fourteen days. The urea clearance returned to its original level in all but one patient.¹ However, the restoration of a normal electrolyte equilibrium did not take place as rapidly as it does when alkali is discontinued in addition to the administration of sodium chloride and fluid. (See Table 4, Part III, p. 56.)

The beneficial effect of sodium chloride on renal function in these patients is an indirect one and seems to be related entirely to the correction of dehydration. Thus, sodium chloride makes it possible to increase the volume of extracellular fluids by extracting water from the cells and by increasing the intake of fluid. The augmented plasma volume, as Gömöri (6), Berenzon

¹See p. 48, n. 1.

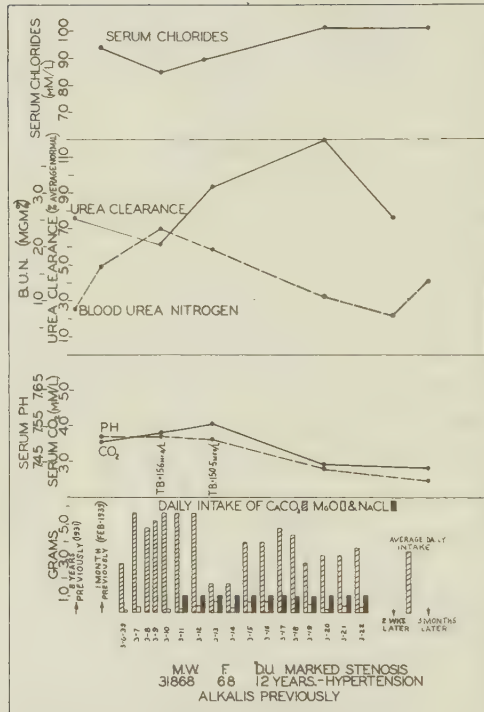


Fig. 2.--Effect of added sodium chloride on acid-base balance and urea clearance during continued calcium carbonate therapy in Case 2.

(7), and others (8) have shown, improves renal function by increasing the rate of circulation and the rate of glomerular filtration.

CONCLUSION

The alkalosis complicating calcium carbonate therapy may be combatted successfully by the administration of adequate

amounts of sodium chloride and fluid even though the ingestion of alkali is continued.

B. THE PROPHYLACTIC VALUE OF SODIUM CHLORIDE

INTRODUCTION

In view of the fact that alkalosis could be treated successfully during continued calcium carbonate ingestion by the addition of adequate quantities of sodium chloride, it seemed desirable to determine the effect of the simultaneous administration of sodium chloride and calcium carbonate on the acid-base balance in a series of patients with peptic ulcer.

METHOD OF STUDY

Sodium chloride and calcium carbonate were given concurrently to 150 patients with peptic ulcer. The series comprised 116 men and 34 women of ages ranging from 24 to 76. The serum CO_2 , pH, and chloride, and the blood urea nitrogen were measured at varying intervals during therapy. Renal function was estimated by the urea clearance test.

RESULTS

Acid-Base Balance

The acid-base balance remained normal except for temporarily increased pH values in 135 of the 150 patients (Table 1). Alkalosis occurred in 15 patients (10.0%). The serum CO_2 ranged from 32.9 to 41.0 mM/L, exceeding 40 mM/L in two instances. The pH varied from 7.47 to 7.63. The lowest serum chloride ranged from 81.3 to 99.7 mM/L; the values were between 81.3 and 90 mM/L in six patients and exceeded 90 mM/L in nine cases. The acid-base disturbance was arbitrarily classified as mild in nine patients, moderate in four, and severe in two.

Clinical Aspects

No direct relationship existed between the amount of calcium carbonate ingested and the development of alkalosis. The

total alkali intake in the 135 patients with normal serum electrolytes ranged from 200 to 500 gms. in 104 and from 500 to 1000 gms. in 27 cases. The remaining four patients of this group had received 1148, 1154, 1850, and 2355 gms. of calcium carbonate, respectively. The total alkali intake in the patients developing alkalosis varied from 200 to 500 gms. in nine and from 500 to 1000 gms. in two cases; four individuals received 1080, 1144, 1305, and 2897 gms. respectively. There was likewise no correlation between the amount of alkali given and the severity of the acid-base disturbance, for the alkalosis was mild in three of the four patients receiving the largest amounts of calcium carbonate.

Nine of the fifteen patients with alkalosis had no complaints referable to the acid-base disturbance. The symptoms in the other six cases consisted of weakness, nausea, headache, dizziness, and mental confusion.

In the group with normal serum electrolytes, massive hemorrhage had occurred in nine; hypertension was present in nine, and polycythemia rubra vera in one. Other complications in the alkalosis group consisted of massive hemorrhage in three, hypertension in six, and atonic bladder with urinary retention, persistent secondary anemia, and perforated ulcer with diabetes in three patients respectively.

Renal Function

The original urea clearance in the patients not developing alkalosis was normal in 94, lowered in 21, and undetermined in 20. Renal function decreased temporarily during combined sodium chloride and calcium carbonate therapy in eight of this group; the original clearance had been normal in six and lowered in two cases.

The urea clearance at the onset of treatment in the alkalosis group was normal in four patients, impaired in five, and undetermined in six. Renal function during alkalosis was not altered significantly in two individuals in whom the urea clearance had been normal originally. Renal function diminished during alkalosis in eight patients; the clearance was below normal at the onset of therapy in four of these. The values in five cases dropped to levels as low as 7, 11, 15, 19, and 20% of average normal. The urea clearance subsequently returned to its original

level in seven of the eight patients (undetermined in one) in whom it had decreased. Renal function was not measured during alkalosis in five cases. (See Tables 2 and 3.)

Blood Urea Nitrogen

The blood urea nitrogen increased during alkalosis in ten patients. The maximum values ranged from 16.2 to 30 mg.% in six and from 35.8 to 97 mg.% in four cases. The highest blood urea nitrogen of 97 mg.% was obtained in a 66-year-old man with hypertension and urinary retention secondary to an atonic bladder. Hypertension was present in the four patients with the highest blood urea nitrogen values. The urine in four cases contained slight to moderate amounts of albumin, and hyaline and granular casts. These findings were present in one patient at the onset of the treatment.

Gastric Retention

A significant difference existed between the patients with normal serum electrolytes and those developing alkalosis with respect to the volume of gastric contents aspirated daily (Table 4). The aspirations averaged less than 200 cc. in 111 patients or 81% of the "normal" group but in only three (20%) of the "alkalosis" group. Large quantities of acid gastric juice thus were removed daily in 12 (80%) of the patients in whom alkalosis occurred. The chloride loss via gastric aspiration appeared to be of considerable importance in the pathogenesis of the hypochloremia and alkalosis since, in these individuals, presumably from 0.5 to 2.0 gms. of chloride ion contained in the gastric contents, as well as a considerable portion of the sodium chloride given orally, were thereby removed each day. In view of the absence of serum electrolyte changes in some patients in whom marked gastric retention also was present, and in whom the salt intake was no greater than that of the patients with alkalosis, it would seem that the chloride loss in the alkalosis group had not been completely replaced by the salt therapy.

Sodium Chloride Therapy

In the normal group the daily salt intake (in addition to the sodium chloride in the diet) averaged from 4 to 5 gms. in 61

patients and from 5 to 10 gms. in 74 individuals. The daily salt intake in the 15 patients developing alkalosis averaged from 3 to 5 gms. in seven and from 5 to 10 gms. in eight cases.

Summary of Patients with Alkalosis

Case 1.--A. F. (Unit no. 217299), a 31-year-old male with a stenosing duodenal ulcer, was found on admission to have a serum CO_2 of 33 mM/L. The blood urea nitrogen and urea clearance were normal. There was a moderately severe secondary anemia. Gastric aspirations averaged 457 cc. daily. A mild chemical alkalosis was detected on the thirteenth day of treatment; the urea clearance decreased moderately during the acid-base disturbance. The serum electrolytes and renal function returned to normal after the daily intake of sodium chloride had been increased from 5-8 to 10 gms.

Case 2.--A. J. (Unit no. 255356), a 43-year-old male, received a total of 2897 gms. of calcium carbonate and magnesium carbonate in 48 days. Gastric aspirations over a period of 41 days averaged 400 cc. daily. A mild chemical alkalosis was noted on the twentieth day; the urea clearance was normal. The intake of sodium chloride was increased from 3-5 gms. to 10 gms. daily and the acid-base balance returned to normal in seven days.

Case 3.--G. K. (Unit no. 76605), a 39-year-old male with diabetes and a large gastric ulcer, was first treated by continuous Wangensteen aspiration of the gastric contents for a period of six days. The serum electrolytes were maintained by parenteral injections of normal saline solution. In the succeeding 44 days, 1305 gms. of calcium carbonate were administered; 10 gms. of sodium chloride were given by mouth daily. The blood urea nitrogen and urea clearance were normal prior to alkali therapy. A mild chemical alkalosis was noted on the thirteenth and twenty-third hospital days. The blood urea nitrogen and urea clearance remained normal, however. Despite the continuation of alkali, the acid-base balance returned to normal.

Case 4.--S. M. (Unit no. 253145), a 43-year-old male, received a total of 588 gms. of calcium carbonate and magnesium carbonate in 20 days. Gastric aspirations over a period of 18 days averaged 400 cc. daily. The original urea clearance was slightly reduced. A moderate alkalosis was noted on the sixth

hospital day; the patient had been vomiting for two days previously. The acid-base disturbance became severe on the twelfth day, the blood urea nitrogen increased to 17.4 mg.% and the urea clearance fell to 43% of average normal. The daily intake of salt was increased from 4-8 gms. to 10 gms. and on the fourteenth day, 200 cc. of a 2% saline solution were given intravenously; calcium carbonate therapy was continued. The serum electrolytes and the blood urea nitrogen returned to normal in seven days; the urea clearance simultaneously returned to its original level.

Case 5.--L. L. (Unit no. 254847), a 45-year-old man with hypertension, was placed on alkali therapy ten days before entry into the hospital and on admission was found to be in mild alkalosis. The blood urea nitrogen three weeks previously had measured 21.4 mg.%; the urea clearance was not determined. The alkalosis became moderately severe after six days, at which time the blood urea nitrogen had risen to 50 mg.% and the urea clearance had decreased to 20%. Gastric aspirations over a period of 14 days had averaged 328 cc. daily. The salt intake was increased from 3-5 gms. to 10 gms. daily and 5% glucose in normal saline was given parenterally for two days; calcium carbonate therapy was continued. The acid-base balance was restored approximately to normal in five days. Three and one-half months later, despite continued alkali therapy, the serum electrolytes were normal; the blood urea nitrogen measured 10.8 mg.% and the urea clearance 65% of average normal.

Case 6.--D. H. S. (Unit no. 259351), a 53-year-old male with hypertension, had experienced a massive hemorrhage from a duodenal ulcer shortly before admission to the hospital. He was markedly anemic. Renal function was not measured prior to alkali therapy. Three hundred and ninety grams of calcium carbonate and magnesium carbonate were given in 17 days. Gastric aspirations averaged 220 cc. daily. A mild chemical alkalosis was noted on the third day; the acid-base disturbance became severe on the fifteenth day at which time the blood urea nitrogen rose to 27 mg.% and the urea clearance decreased to 20%. In addition to the 10 gms. of sodium chloride taken by mouth daily, large amounts of normal saline solution were given parenterally on the third, seventh, sixteenth, seventeenth, and eighteenth days. The acid-base balance on the twenty-second day was normal despite the continued ingestion of alkali. Three weeks later the blood urea

nitrogen measured 13.5 mg.% and the urea clearance 70% of average normal.

Case 7.--P. L. (Unit no. 261811), a 40-year-old male with a stenosing duodenal ulcer and hypertension, was found on admission to be in mild alkalosis. The acid-base balance was restored to normal after three infusions of 1500 cc. of normal saline solution. Four hundred and fourteen grams of calcium and magnesium carbonate were given subsequently. Gastric aspirations averaged 800 cc. daily. Eight grams of sodium chloride were given by mouth daily. A mild chemical alkalosis was noted on the seventh day of alkali therapy but the serum electrolytes returned to normal without additional treatment.

Case 8.--F. S. (Unit no. 240652), a 54-year-old male with a stenosing duodenal ulcer, developed a moderately severe alkalosis on the fourth day of treatment. Gastric aspirations had averaged 490 cc. daily. Renal function was not measured prior to therapy; during alkalosis, however, the urea clearance was only slightly below normal. The acid-base balance was partially restored after the intake of sodium chloride by mouth had been increased from 5 to 15 gms. daily and normal saline solution had been administered on the fourth and fifth hospital days. Tricalsate was substituted for the calcium carbonate on the fourteenth day with a return of the serum electrolytes to normal. The blood urea nitrogen and the urea clearance after subsidence of the alkalosis were normal.

Case 9.--F. O'T. (Unit no. 153776), a 53-year-old man with syphilis and hypertension, had vomited frequently prior to admission into the hospital. Three hundred and twenty-eight grams of calcium and magnesium carbonate were given in 11 days. Gastric aspirations averaged 195 cc. daily. Renal function was not measured prior to alkali therapy. A mild chemical alkalosis was noted on the ninth day; the blood urea nitrogen increased to 24.8 mg.% and the urea clearance dropped to 10% of average normal. Alkali was discontinued for three days and the daily salt intake was increased from 5 to 10 gms.; 3000 and 1300 cc. of normal saline solution were administered parenterally on two occasions. The acid-base balance returned to normal and was not altered after the resumption of calcium carbonate therapy.

Case 10.--J. McI. (Unit no. 257100), a 41-year-old male with syphilis and hypertension, had taken large amounts of sodium

bicarbonate for the relief of ulcer symptoms. The blood urea nitrogen on entry measured 23.3 mg.% and the urea clearance 60% of average normal. Two hundred and twelve grams of calcium and magnesium carbonate were given during the first seventeen days; 3 gms. of sodium chloride were taken by mouth daily. Gastric aspirations averaged 230 cc. daily. A moderately severe alkalosis was noted on the sixth day of treatment. The blood urea nitrogen measured 29.8 mg.% and the urea clearance 22%. Fifteen hundred to 3000 cc. of normal saline were given daily from the sixth to the tenth day. Calcium carbonate was discontinued and aluminum hydroxide was administered during the next 16 days. The acid-base balance returned to normal although the blood urea nitrogen continued to range from 18.2 to 27.0 mg.%. Calcium carbonate therapy was resumed on the thirty-fourth hospital day; 6 gms. of sodium chloride were given by mouth daily. The serum electrolytes remained normal except for a slight elevation of the serum CO_2 (32.8 mM/L). One month later the blood urea nitrogen measured 20.7 mg.% and the urea clearance 40% of average normal.

Case 11.--T. D. (Unit no. 256095), a 66-year-old male, entered the hospital because of a massive hemorrhage from a duodenal ulcer. Seven blood transfusions and 1,144 gms. of calcium and magnesium carbonate were administered in 29 days. Five gms. of sodium chloride were given by mouth daily. The clinical course was complicated by the development of an atonic bladder with urinary retention. A mild alkalosis was noted on the second hospital day. The alkalosis became severe on the twenty-sixth day. At this time the blood urea nitrogen rose to 97 mg.% and the urea clearance diminished to 7% of average normal (renal function had been low originally). Gastric aspirations between the twenty-first and thirty-first days averaged 502 cc. daily. The serum electrolytes returned to normal after the daily administration of 3000 cc. of 5% glucose in normal saline and normal saline solutions. Alkali therapy and gastric aspiration were discontinued on the thirty-first hospital day. The blood urea nitrogen gradually decreased to 12.8 mg.% and the urea clearance one month later rose to 60% of average normal, its original level.

Case 12.--F. C. (Unit no. 257481), a 48-year-old male with hypertension, was admitted to the hospital with a massive hemorrhage from a duodenal ulcer. Seven hundred and thirty-four grams of calcium and magnesium carbonate were given in 29 days.

Gastric aspirations averaged 168 cc. daily. The original urea clearance was slightly below normal. Symptoms suggestive of alkalosis were noted on the twenty-fourth hospital day, at which time the daily intake of sodium chloride was increased from 3-6 to 10 gms. A mild chemical alkalosis was noted on the twenty-sixth day, and 1500 cc. of normal saline solution were given parenterally. Calcium carbonate was discontinued on the thirtieth day at which time the blood urea nitrogen measured 31.2 mg.% and the urea clearance 15% of average normal. The blood urea nitrogen returned to normal and the urea clearance to its original level several weeks later.

Case 13.--L. B. (Unit no. 256277), a 48-year-old male, had been vomiting frequently for six to seven months. The urea clearance was not determined before therapy. Gastric aspirations over a period of 20 days averaged 300 cc. daily. A severe alkalosis was noted on the ninth day; the daily intake of sodium chloride was increased from 5 to 8 gms. with prompt clinical relief.

Case 14.--H. F. (Unit no. 261987), a 55-year-old male, had vomited frequently before hospitalization. Large amounts of gastric contents were aspirated daily. The original urea clearance was low. A mild alkalosis was noted on the eleventh hospital day. The intake of sodium chloride was maintained at a level of 10 gms. daily. There were no clinical symptoms. The acid-base balance was not determined subsequently.

Case 15.--J. G. (Unit no. 271789), a 44-year-old male with normal renal function, was found to have a mild chemical alkalosis on the eighth day. The serum electrolytes were not measured subsequently. There were no clinical symptoms.

COMMENT

The results of this investigation indicate that alkalosis complicating calcium carbonate therapy can be prevented in almost all patients by the concurrent administration of adequate amounts of sodium chloride. The therapeutic action of sodium chloride is probably attributable (a) to the replacement of chloride ion lost by the aspiration of gastric contents, and (b) to the increased excretion of base bicarbonate in the urine at the expense of the blood bicarbonate after the administration of salt. The experi-

mental observations of Schoenthal (9) are of particular importance in this connection. Hartman and Smyth (10) had shown previously that in the presence of an increased plasma bicarbonate secondary to chloride loss, the administration of sodium chloride leads to the excretion of bicarbonate in the urine. Schoenthal gave six healthy infants from 6 to 10 gms. of sodium chloride daily, distributed equally in the feedings over a period of one to four days. An increase in the chloride concentration of the serum of from 6 to 15% was observed in all cases. The plasma bicarbonate decreased moderately in four cases, and the reaction of the plasma in three patients tended to shift toward the acid side. The excretion of base bicarbonate in the urine was usually increased and accompanied by a rise in pH as shown in Table 5.

There was naturally an increase in the urinary chloride but this did not equal the intake. These findings are in agreement with the observations of György (11) in his study of the excretion of acid in infants after the administration of salt.

It should be noted that in several patients of the present series, sodium chloride therapy was apparently not only inadequate to forestall the development of alkalosis but also insufficient to correct the acid-base disturbance. It is possible that in these few individuals, insufficient amounts of salt were given and also that the excretion of bicarbonate in the urine was retarded by the antecedent impairment of renal function.

CONCLUSIONS

1. The simultaneous administration of sodium chloride with alkali therapy (calcium carbonate) decreased the incidence of alkalosis from 30% to 10%.

2. Alkalosis during alkali therapy can be prevented in almost all cases by the administration of sufficient amounts of sodium chloride and fluid to prevent the development of hypochloremia and the accumulation of bicarbonate in the blood.

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TABLE 1

ACID-BASE BALANCE DURING SIMULTANEOUS ADMINISTRATION
OF SODIUM CHLORIDE AND CALCIUM CARBONATE
(150 PATIENTS)

	Serum CO ₂ (mM/L)	Serum pH	Serum Cl (mM/L)
No alkalosis (135 patients)	22-30	7.35-7.50	95-105
Alkalosis (15 patients)	32.9-41.0	7.47-7.63	81.3-99.7

TABLE 2

UREA CLEARANCE AT ONSET OF SODIUM CHLORIDE-
CALCIUM CARBONATE THERAPY

Urea Clearance	Patients Not Developing Alkalosis	Patients Developing Alkalosis
(a) Normal	94	4
(b) Lowered	21	5
(c) Undetermined	20	6
Totals	135	15

TABLE 3

UREA CLEARANCE DURING SODIUM CHLORIDE-
CALCIUM CARBONATE THERAPY

Urea Clearance	No Alkalosis	Alkalosis
(a) Unchanged ..	92	2
(b) Reduced	8	8
(c) Undetermined	35	5
Totals	135	15

TABLE 4
GASTRIC RETENTION

Volume (cc.)	No Alkalosis	Alkalosis
0-100	81	0
100-200	30	3
200-300	12	3
300-400	9	2
400-500	1	5
500-	2	2
Totals	135	15

TABLE 5

pH OF URINE BEFORE AND AFTER ADMINISTRATION OF
SODIUM CHLORIDE IN SIX NORMAL INFANTS*

<u>Before</u>	<u>After</u>
5.80	7.35
6.75	6.40
6.75	7.10
6.35	6.75
5.90	6.00

*Taken from Schoenthal (9).

PART V. THE EFFECT OF CALCIUM CARBONATE, ALUMINUM
PHOSPHATE, AND ALUMINUM HYDROXIDE ON
MINERAL EXCRETION IN MAN

INTRODUCTION

In order to elucidate further the mechanism of the alkalosis described in preceding sections, a more detailed study of mineral excretion following the administration of relatively non-absorbable compounds seemed desirable. Hence an investigation of the effect of calcium carbonate, aluminum phosphate, and aluminum hydroxide was undertaken.

METHOD OF STUDY

Detailed studies were carried out in two adult men and one woman with peptic ulcer in all of whom previous observations had indicated renal function to be satisfactory. A special metabolic ward and nursing staff were utilized. The patients were maintained on special ulcer diets (Tables 1 and 2) without change during the entire experiment. Chloride-free distilled water was used for drinking purposes. The fluid intake and urinary output were recorded daily. The body weight was measured every one to two days. The only medication permitted, aside from the substances studied, was the occasional administration of cascara to facilitate daily bowel activity,¹ and the use of mild sedatives for sleep. An interval of four to six days was allowed for adjustment to the diet prior to the control observation. Mineral excretion was studied over periods each of four days' duration. Ten grains of carmine were given at the onset of each period and repeated 96 hours later; the feces obtained between the carmine markers was collected for analysis. The four-day collection was mixed thoroughly; accurately weighed 2.0 gms. samples were taken for the various determinations. All analyses were done in duplicate or triplicate.

The chemical studies of the feces were carried out as follows: The calcium content was determined by first boiling the sample with concentrated nitric acid and potassium permanganate. After cooling, the mixture was diluted with distilled water to

¹There was no instance of diarrhea.

100 (or 200) cc. volume and adjusted to the proper pH (4.6-5.2) using Brom Cresol green as indicator. The procedure then followed was the same employed for blood serum (1). (Calculation:

$$\frac{\text{Titer} \times 10}{2} \text{ equals mg. Ca per 1 gm. feces.})$$

For determining the chloride content, 5.0 cc. of a 0.1 N solution of silver nitrate were added to 2.0 gm. samples of feces and the mixture allowed to stand for several hours. Digestion then was carried out as with the calcium analysis. The mixtures were cooled, 5% ferric alum added as indicator, and then titrated with a 0.1 N solution of potassium thiocyanate. (Calculation:

$$\frac{5 - \text{titer} \times 3.5}{2} \text{ equals mg. chloride ion in 1.0 gm. feces.})$$

The phosphate in the feces was determined in Case 1 by wet ashing of the samples with nitric and sulphuric acids and, when necessary, superoxal. The mixtures then were cooled, adjusted to known volume with distilled water, and the phosphate content measured by the Fiske-Subbarow method (2) as adapted for the Evelyn photoelectric colorimeter. In Cases 2 and 3 the samples of feces were ashed in a muffle furnace and the analyses then carried out as above.

In Case 3 the sodium content of the feces was measured by the following procedure: 20 cc. of ferric sulphate and 3 cc. of concentrated sulphuric acid were added to 10 gm. samples. The mixtures were dried in an oven and then ashed in a muffle furnace. The ash was taken up in 10 cc. of distilled water and 3 cc. aliquots analyzed for sodium by the method employed for blood (3).

The potassium content of the feces in Case 3 was determined as follows: 2.0 gm. samples of feces were dried in an oven and then ashed in a muffle furnace. The ash was taken up in 10 cc. of distilled water and 1.0 cc. aliquots analyzed by the procedure used for blood (4).

Twenty-four hour collections of urine were obtained throughout the study. The urine was voided directly into a bottle containing toluene as a preservative and a layer of mineral oil to prevent the escape of CO₂ (5). The urine was kept in an ice-box and analyzed at the end of each collection for the following: (a) pH, using the Beckman pH meter, (b) chloride (6), (c) calcium, (d) phosphate, and (e) amino-nitrogen plus ammonium salts (7).¹

¹Referred to in the text as "ammonia" for the purpose of simplicity.

The sodium content of the urine in Case 3 was measured by the same technique employed for blood, modified as to the volume used; ferric salt was added in amounts sufficient to prevent interference by phosphates. The urinary potassium was determined as follows: 2.0 cc. samples of urine were ashed in a muffle furnace and the ash taken up in 10 cc. of distilled water; 2.0 cc. aliquots then were concentrated and analyzed by the method employed for blood.

Simultaneous studies were made of the serum electrolytes. Venous blood drawn under oil was utilized for the following analyses: chloride, CO_2 (8), pH (9), calcium, and phosphorus. Oxalated blood was used for the measurement of the blood urea nitrogen (10). The following additional data were obtained in Case 3: cell volume, serum water (11), blood sodium, potassium, and total base (12), and the urea clearance (13).

After control values had been established, the effects of calcium carbonate, aluminum phosphate, and aluminum hydroxide were studied in individual periods. A four-to-five-day interval for adjustment to the added medication was allowed prior to the analyses. Calcium carbonate was administered in 2.0 gm. amounts ten times daily; 80 gms. were thus given in a four-day period, containing 32 gms. of calcium ion. One hundred and five cc. of aluminum phosphate were administered daily in divided doses; a total of 420 cc. in a four-day period containing, by analysis, 386 mg. of chloride, 4368 mg. of phosphate, and 2625 mg. of aluminum (14). One hundred and five cc. of aluminum hydroxide were given daily in divided doses; a total of 420 cc. in a four-day period containing 386 mg. of chloride and 4716 mg. of aluminum. Complete mineral balances were not obtained since no attempt was made to measure the loss in the insensible perspiration or sweat. This loss presumably was constant, however, through the various periods in each case since fairly constant conditions were maintained. The results are considered chiefly in relation to the individual control values.

RESULTS

Case 1 (Table 3, Fig. 1).--The observations in this patient were obtained during March, April, and May, 1941. The amount of chloride excreted during the control period was less

than chloride intake. The calcium output slightly exceeded calcium intake. The phosphate balance was practically in equilibrium; 65% of the total output appeared in the urine. The acid-base balance of the blood was normal.

The administration of calcium carbonate resulted in a slight elevation of the pH of the urine and a decrease in the output of ammonia. Chloride excretion in the urine appeared to be markedly diminished; the lowered chloride output persisted for four days after discontinuation of the alkali. Chloride excretion in the feces increased slightly. The calcium content of the urine rose; total calcium excretion exceeded calcium intake. The phosphate content of the urine dropped, constituting only 33% of the total output. Phosphate excretion in the feces increased but the phosphate balance was positive. The serum electrolytes remained normal. The patient gained two pounds during this period.

Aluminum phosphate produced no change in the acid-base equilibrium of the blood. The pH of the urine was slightly less than the control value. The output of ammonia was augmented. The chloride content of the urine exceeded control levels, but since the aluminum phosphate had been given after calcium carbonate, the excess may represent a portion of the chloride retained during the calcium carbonate period. The chloride output in the feces increased slightly. Calcium excretion was not altered significantly. The phosphate content of the urine was unchanged and almost all of the additional phosphate administered at this time appeared in the feces; the phosphate balance was slightly positive.

Aluminum hydroxide did not alter the acid-base equilibrium of the blood, thus confirming previous observations (15). The pH of the urine rose slightly, while the output of ammonia decreased. The chloride content of the urine was slightly below the control level; the chloride output in the feces rose slightly. Calcium excretion was unchanged. The phosphate content of the urine decreased markedly, comprising only 18% of the total output; this finding is in agreement with the observations of Fauley et al. and of Freeman (16). Although the amount of phosphate in the feces increased considerably, the total output was not augmented.

Case 2 (Table 4, Fig. 2).--The observations in this patient were obtained during July and August, 1941. The chloride

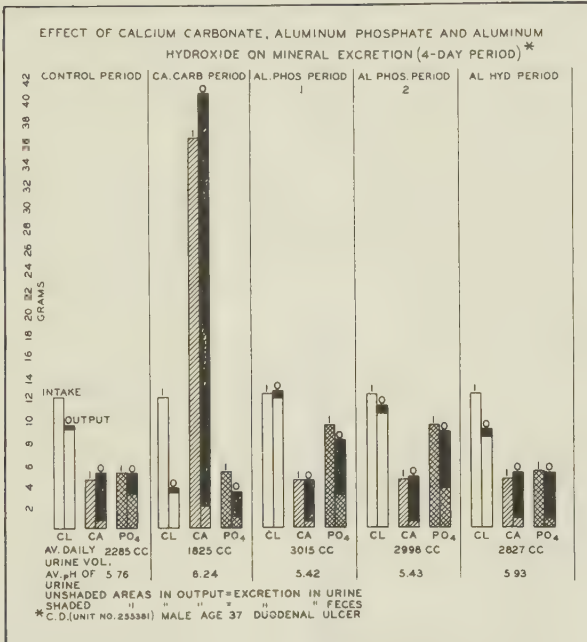


Fig. 1.--The effect of calcium carbonate, aluminum phosphate, and aluminum hydroxide on mineral excretion in Case 1.

output during the control period was less than chloride intake; the positive balance, however, was smaller than in Case 1. Calcium and phosphate excretion slightly exceeded the intake of these ions. Fifty-eight per cent of the total phosphate output appeared in the urine.

The administration of calcium carbonate was followed by an increase in the urinary pH and by a marked decrease in the output of ammonia. Chloride excretion in the urine diminished, but

to a lesser degree than was noted in Case 1; it persisted for six days after discontinuation of the alkali. The chloride content of the feces increased slightly. The urinary calcium was elevated; the total calcium output exceeded the intake. The urinary phosphate decreased markedly, accounting for only 22% of the total amount excreted. The phosphate content of the feces rose, but there was no loss of phosphate from the body. The acid-base balance remained normal. The patient gained one and one-half pounds during this period.

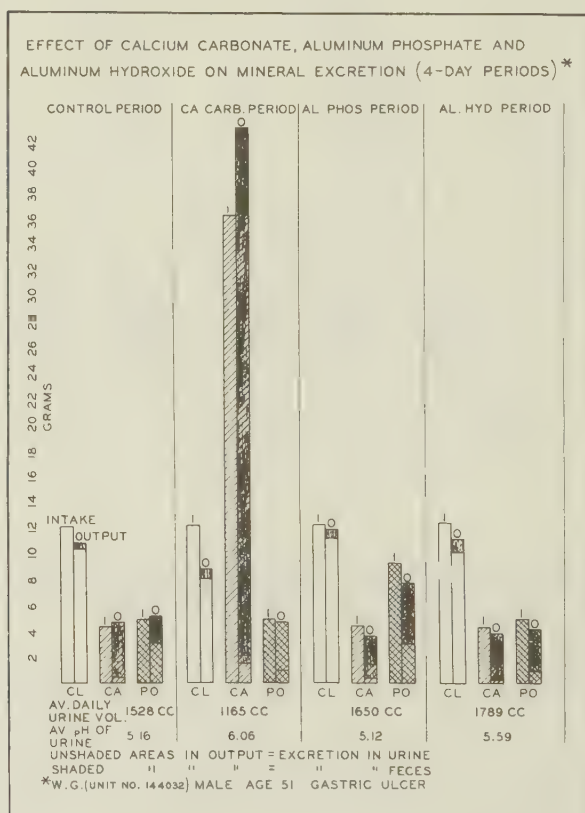


Fig. 2.--The effect of calcium carbonate, aluminum phosphate, and aluminum hydroxide on mineral excretion in Case 2.

Aluminum phosphate did not alter the acid-base equilibrium of the blood. The urinary ammonia increased slightly. The chloride content of the urine and feces slightly exceeded control values. The amount of phosphate in the urine was unchanged from the control period and practically all of the additional phosphate administered during this period was recovered in the feces.

The acid-base balance of the blood remained normal during aluminum hydroxide therapy. The pH of the urine increased slightly, while the output of ammonia diminished. Except for a slight rise in the chloride content of the feces, chloride excretion closely approximated the control values. Calcium excretion likewise did not change significantly. The urinary phosphate decreased, comprising only 22% of the total output. Although the phosphate content of the feces increased, the balance of this mineral was slightly positive.

Case 3 (Table 5, Fig. 3).--The observations in this patient were limited to a study of the effect of calcium carbonate and were obtained during November and December, 1941, and January, 1942. Chloride excretion varied slightly during the three control periods but the output usually balanced the intake. Sodium was excreted almost entirely via the urine; the quantity recovered, however, was considerably less than the intake. Potassium also was excreted for the most part in the urine. The potassium balance was slightly positive.¹ The calcium output was slightly below the calcium intake. The phosphate balances were practically in equilibrium; 73% to 75% of the total phosphate output appeared in the urine.

The administration of calcium carbonate resulted in a slight elevation of the urinary pH and a decrease in the output of ammonia. The chloride content of the urine closely approximated control values, thereby differing from the results obtained in the preceding cases. The excretion of sodium was not altered appreciably. The potassium content of the urine decreased slightly; the potassium output in the feces approximated control values; these changes were minimal and not considered significant. The calcium content of the urine increased but the total amount of calcium recovered was definitely less than the intake. Phos-

¹There was no loss of sodium or potassium during the analytical procedure; the methods were found to be almost 100% accurate in recovery experiments on material provided by Dr. K. Knowlton.

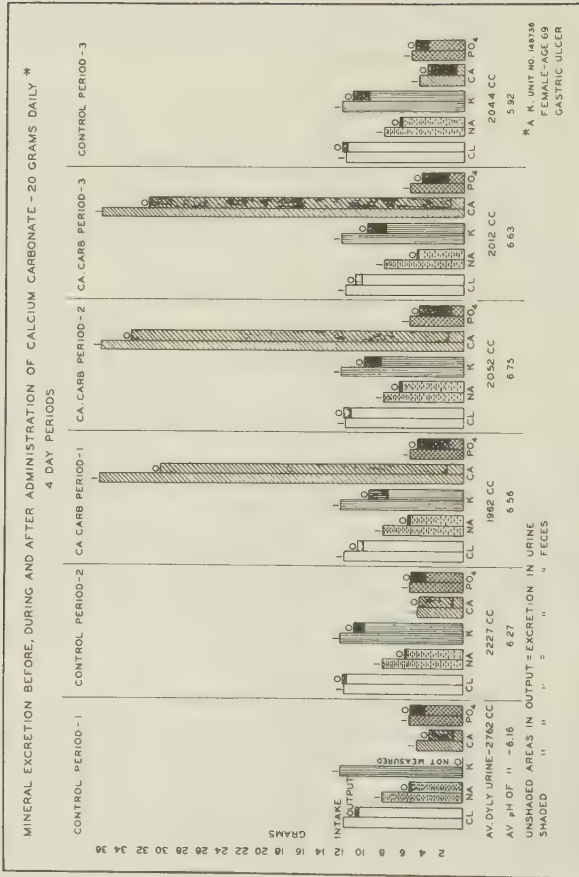


Fig. 3.--Mineral excretion before, during, and after administration of 20 Gms. calcium carbonate daily (Case 3).

phate excretion in the urine decreased, accounting for only 29% to 38% of the total output. The phosphate content of the feces increased considerably, but the phosphate balance was slightly positive. As in the preceding patients, the serum electrolytes remained normal. The cell volume, serum water, and urea clearance were not altered significantly.

The changes in mineral excretion induced by calcium carbonate occurred within 24 hours after the addition of the alkali to the regimen. Mineral excretion returned to original levels almost equally soon after the discontinuation of calcium carbonate therapy, although in two of the three patients studied, the diminished output of chloride and ammonia in the urine persisted for several days.

COMMENT

It will be noted that, despite fairly similar diets, mineral excretion varied in all three cases. This difference was manifested chiefly in the excretion of chloride and may be related to an individual variation in the loss of chloride in the sweat. The varied calcium balances during calcium carbonate therapy seem to be within the range of experimental error, although differing responses to a given intake of calcium have been reported by other workers (17). The changes in mineral excretion induced by calcium carbonate were more pronounced than those of aluminum phosphate or aluminum hydroxide. They consisted of a marked decrease in the ammonia and phosphate content of the urine and, in two patients, of the chloride content as well. The urinary excretion of calcium rose. The output of phosphate in the feces increased markedly, although the phosphate balance remained positive. Potassium excretion in the urine diminished slightly. Diminution of ammonia and chloride excretion have been reported also after the use of sodium bicarbonate (18). The retention of chloride during calcium carbonate ingestion in two of the three patients studied was of interest. Although it was not observed in Case 3, it has been noted in other patients receiving calcium carbonate (see Table 6).

In the one patient in whom determinations of the potassium, sodium, and total base were obtained, no retention of base was observed; however, no significant retention of chloride had

occurred in this particular case. Similarly, no increase in the total base has been found in numerous additional patients receiving calcium carbonate in the course of ulcer therapy.

The diminished excretion of phosphate in the urine and its increased output in the feces are familiar observations (19) and are attributable to the formation in the intestine of insoluble calcium phosphate. The moderate increase in urinary pH denotes presumably an elevation in the bicarbonate content of the urine.¹ The elevated pH may be related in part to the diminished concentration of phosphate in the urine. This possibility is suggested by the observation that the urinary pH increased during aluminum hydroxide therapy, at which time the urinary phosphate was reduced in a degree similar to that observed with calcium carbonate. Another possibility may be the formation, absorption, and subsequent excretion in the urine of small amounts of calcium bicarbonate. It is of considerable interest to note that calcium carbonate does not increase the pH of the urine in the absence of free hydrochloric acid in the stomach, as shown in Table 7.

This difference in response to calcium carbonate may be related to the possibility that the phosphate content of the urine is not reduced in patients with achlorhydria.

It should be emphasized that the changes in mineral excretion observed with calcium carbonate in these experiments were not of sufficient magnitude to produce an alkaline urine or to disturb the acid-base equilibrium of the blood.

The influence of aluminum phosphate on mineral excretion was negligible. Aluminum hydroxide diverted phosphate excretion from the urine to the feces as a result of the formation in the intestine of insoluble aluminum phosphate. Similar findings have been described with other preparations of aluminum (21). The total excretion of phosphate was not affected significantly and no alteration in the serum phosphorus was observed.

All three compounds increased the output of chloride in the feces to a similar degree. Chloride loss by this route, however, was very slight and obviously can be of no importance.

¹The hydrogen-ion concentration of the urine, according to Gamble (20), is determined mainly by the ratio $\frac{H.HCO_3}{B.HCO_3}$. Inasmuch as the $H.HCO_3$ has a nearly stationary concentration regardless of the reaction of the urine, an increase in pH indicates an increase in bicarbonate.

CONCLUSIONS

1. Moderate amounts of calcium carbonate given orally to humans diminish the acidity of the urine, lower markedly its phosphate content, and, in some cases, its chloride content also. The urinary calcium rises. The excretion of sodium is not altered significantly. The potassium content of the urine diminishes slightly. Phosphate excretion in the feces is elevated. There is a slight but insignificant loss of chloride in the feces. These alterations in mineral excretion are not associated with alkalosis.

2. Large amounts of aluminum phosphate given orally to humans increase slightly the chloride content of the feces, but otherwise do not affect mineral excretion. The acid-base balance of the blood is undisturbed.

3. Large amounts of aluminum hydroxide given orally to humans decrease the acidity of the urine and diminish markedly its phosphate content. The urinary output of chloride decreases slightly in some cases, while chloride excretion in the feces increases slightly. The phosphate content of the feces is elevated but the total excretion of phosphate is not increased. These changes in mineral excretion do not alter the acid-base equilibrium of the blood.

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TABLE 1

COMPOSITION OF DIET EMPLOYED IN CASES 1 AND 2
(DAILY VALUES)

	Special Diet	Standard Values 70 Kilo Adult Male
Carbohydrate	266	...
Protein	58	...
Fat	163	...
Calories	2763	...
Chloride (mg.)	3047	...
Sodium (mg.)	2014	...
Calcium (mg.)	1140	800
Phosphate (mg.) ...	1300	1320
Iron (mg.)	7	12
Vitamin A (I.U.) ..	6200	5000
Thiamin (mg.)	1.0	1.5
Riboflavin (mg.) ..	1.2-2.4	2.2
Ascorbic acid (mg.)	5-30	75
Vitamin D (I.U.) ..	160-385	...

TABLE 2

COMPOSITION OF DIET EMPLOYED IN CASE 3
(DAILY VALUES)

	Special Diet	Standard Values for Sedentary Adult Female
Carbohydrate	198	...
Protein	72	...
Fat	104	...
Calories	2016	...
Chloride (mg.)	2974	...
Sodium (mg.)	2029	...
Potassium (mg.) ...	3052	...
Calcium (mg.)	1159	800
Phosphate (mg.) ...	1342	1320
Iron (mg.)	10.5	12
Vitamin A (I.U.) ..	9570	5000
Thiamin (mg.)	1.014	1.2
Riboflavin (mg.) ..	2.51	1.8
Ascorbic acid (mg.)	78	70
Vitamin D (I.U.) ..	38	...

TABLE 3

EFFECT OF CALCIUM CARBONATE, ALUMINUM PHOSPHATE, AND ALUMINUM HYDROXIDE
ON THE ACID-BASE BALANCE OF THE BLOOD AND ON MINERAL EXCRETION

Case 1. C. D., 255381. Male, Age 37. Duodenal Ulcer.

	Total 4-Day Intake (mg.)			Acid-Base Balance of Blood							Excretion in Urine				
	Cl	Ca	PO ₄	Cl mM/L	CO ₂ mM/L	pH	B.U.N. mg.%	Ca m.Eq./L	P mM/L	Avg. Daily Vol. cc.	Avg. pH	4-Day Output (mg.)			
												Cl	Ca	PO ₄ NH ₄	
I. Control Period	12,188	4,560	5200	101.7	29.6	7.46	9.4	5.05	1.32	2238	5.76	9,344	964	3319 4858	
II. Calcium Carbonate	12,188	36,560	5200	99.6	29.6	7.46	13.5	5.15	0.97	1825	6.24	3,327 { ?}	2070	1108 2667	
III. Aluminum Phosphate(A)	12,574	4,560	9568	103.4	28.4	7.48	12.0	5.7	1.0	3015	5.42	12,208	758	3035 6364 9	
IV. Aluminum Phosphate(B)	12,574	4,560	9568	100.5	29.8	7.46	10.0	5.5	1.22	2998	5.43	10,631	712	3676 5557	
V. Aluminum Hydroxide	12,574	4,560	5200	102.4	28.5	7.47	15.4	5.25	1.13	2827	5.93	8,482	971	908 3370	

Control period obtained after patient had been on special diet for 4 days.

Calcium carbonate (20 Gms. daily) given for 4 days prior to analyses.

Aluminum phosphate (105 cc. daily) given for 4 days prior to analyses; second

aluminum phosphate period obtained after patient had received 105 cc. of

this preparation daily for 11 days.

Aluminum hydroxide (105 cc. daily) given for 4 days prior to analyses.

The patient's body weight during the entire study increased from 53 to 54.8 kg.

The daily fluid intake was 2430 cc. during first two periods, 3030 cc. during

third period, and 3230 cc. thereafter.

TABLE 3--Continued

	Excretion in Feces			Total 4-Day Output (mg.)				Mineral Balance per 4-Day Period (mg.)			
	4-Day Output (mg.)			Cl	Ca	PO ₄	PO ₄	Cl	Ca	PO ₄	
	Cl	Ca	PO ₄								
I. Control Period	343	4,342	1783	9,687	5,306	5102	5102	+2501	- 746	+ 98	
II. Calcium Carbonate	399	38,760	2242	3,726	40,830	3350	3350	+8462(?)	-4270	+1850	
III. Aluminum Phosphate(A)	602	3,698	5100	12,810	4,456	8135	8135	- 236	+ 4	+1433	
IV. Aluminum Phosphate(B)	649	4,110	5302	11,280	4,822	8978	8978	+1294	- 262	+ 590	
V. Aluminum Hydroxide	542	4,155	4128	9,024	5,126	5036	5036	+3550	- 666	+ 164	

TABLE 4

EFFECT OF CALCIUM CARBONATE, ALUMINUM PHOSPHATE, AND ALUMINUM HYDROXIDE
ON THE ACID-BASE BALANCE OF THE BLOOD AND ON MINERAL EXCRETION

Case 2. W. G., 144032. Male, Age 51. Gastric Ulcer.

	Total 4-Day Intake (mg.)			Acid-Base Balance of Blood						Excretion in Urine				
	Cl	Ca	PO ₄	Cl mM/L	CO ₂ mM/L	pH	B.U.N. mg. %	Ca m.Eq./L	P mM/L	Avg. Daily Vol. cc.	Avg. pH	4-Day Output (mg.)		
I. Control Period	12,120	4,400	5000	96.7	28.6	7.43	14.2	4.65	1.42	1528	5.16	10,500	505	3041 5253
II. Calcium Carbonate	12,120	36,400	5000	95.6	29.9	7.43	13.8	5.1	1.35	1165	6.06	8,095	1632	1018 2800 3
III. Aluminum Phosphate	12,506	4,400	9368	106.9	28.2	7.42	16.3	4.75	1.40	1650	5.12	11,279	443	3040 6248
IV. Aluminum Hydroxide	12,506	4,400	5000	101.6	27.4	7.41	14.0	5.05	1.40	1789	5.59	10,264	443	999 3117

Control period obtained after patient had been on special diet for 5 days.
 Calcium carbonate (20 gms. daily) given for 4 days prior to analyses.
 Aluminum phosphate (105 cc. daily) given for 4 days prior to analyses.
 Aluminum hydroxide (105 cc. daily) given for 4 days prior to analyses.
 The patient's body weight during the entire study increased from 54.2 to 55.7 kg.
 The daily fluid intake was 1830 cc. during the first two periods and 2730 cc. thereafter.

TABLE 4--Continued

	Excretion in Feces			Total 4-Day Output (mg.)			Mineral Balance per 4-Day Period (mg.)		
	4-Day Output (mg.)			Cl	Ca	PO ₄	Cl	Ca	PO ₄
	Cl	Ca	PO ₄						
I. Control Period	407	4,342	2171	10,907	4,847	5212	+1213	- 447	- 212
II. Calcium Carbonate	745	41,557	3760	8,850	43,189	4778	+3270	-6789	+ 222
III. Aluminum Phosphate	656	3,222	4796	11,935	3,665	7836	+ 571	+ 735	+1532
IV. Aluminum Hydroxide	675	3,508	3098	11,039	3,951	4097	+1467	+ 449	+ 903

TABLE 5

MINERAL EXCRETION BEFORE, DURING, AND AFTER ADMINISTRATION OF CALCIUM CARBONATE

Case 3. A. K., 148736. Female, Age 69. Gastric Ulcer.

	Total 4-Day Intake (mg.)					Acid-Base Balance of Blood									
	Cl	Na	K	Ca	PO ₄	Cl	CO ₂	pH	BUN.	Urea	Ca	P	K	Na	Total
						mM/L	mM/L		mg. %	Clear- ance % Avg. Normal	m.Eq/L	mM/L	m.Eq/L	m.Eq/L	m.Eq/L
Control Period I	11,896	8000	12,208	4,636	5368	102.2 102.2	31.5 30.3	7.45 7.41	15.4 15.5	70 61	5.1 4.7	1.26 1.26	5.25 5.35	140.3 145.7	153.2 157.5
Control Period II	11,896	8000	12,208	4,636	5368	102.2	31.8	7.47	14.6	81	4.7	1.29	5.20	144.3	153.3
Calcium Carbonate Period I	11,896	8000	12,208	36,636	5368	100.7	31.7	7.50	17.0	44	5.75	1.35	5.20	147.9	160.0
Calcium Carbonate Period II	11,896	8000	12,208	36,636	5368	100.5	31.9	7.44	17.8	65	5.35	1.19	5.00	145.2	158.5
Calcium Carbonate Period III	11,896	8000	12,208	36,636	5368	103.1	29.7	7.47	15.5	65	5.1	1.22	5.30	145.0	156.1
Control Period III	11,896	8000	12,208	4,636	5368	100.2	30.9	7.43	13.2	76	5.1	1.13	5.30	143.8	

Control periods obtained after patient had been on special diet for 6 days.

Calcium Carbonate Period I obtained after administration of 20 gms. CaCO₃ daily for 5 days prior to analyses.

Calcium Carbonate Period II obtained after 13 days of calcium carbonate therapy.

Calcium Carbonate Period III obtained after calcium carbonate had been discontinued for 9 days.

The daily fluid intake was 3000 cc. for the first 12 days and was then maintained at 2000 cc. daily for the remainder of the study.

TABLE 5--Continued

	Cell Vol. %	Serum Water gm. %	Body Weight kg.	Excretion in Urine						Excretion in Feces					
				Avg. Daily Vol. cc.	Avg. pH	4-Day Output (mg.)						4-Day Output (mg.)			
						Cl	Na	K	Ca	PO ₄	NH ₄	Cl	Na	K	Ca PO ₄
Control Period I	42.0 38.8	90.78 91.41	59.1	2762	6.16	10,199	5010		925	3868	2468	282	118		2,443 1298
Control Period II	37.0	90.97	59.3	2227	6.27	11,630	5438	9867	991	3784	2561	282	85	1036	3,304 1354
Calcium Carbonate Period I	41.0	90.42	59.5	1962	6.56	9,951	5412	7656	1622	1498	1484	569	153	1866	28,482 3091
Calcium Carbonate Period II	41.5	90.68	59.6	2052	6.75	11,385	6373	8134	1607	1281	1516	548	173	1853	31,498 3081
Calcium Carbonate Period III	37.5	91.14	59.8	2012	6.63	10,227	4564	7845	1399	1577	1888	566	64	1880	30,188 2541
Control Period III	37.2	91.06	60.5	2044	5.92	11,842	6498	9498	690	3772	2638	373	187	1659	3,098 1202

TABLE 5--Continued

	Total 4-Day Output (mg.)					Mineral Balance per 4-Day Period (mg.)				
	Cl	Na	K	Ca	PO ₄	Cl	Na	K	Ca	PO ₄
Control Period I	10,481	5228		3,368	5166	+1415	+2772		+1268	+ 202
Control Period II	11,912	5523	10,903	4,295	5138	- 16	+2477	+1305	+ 341	+ 230
Calcium Carbonate Period I	10,520	5565	9,522	30,104	4589	+1376	+2435	+2686	+6532	+ 779
Calcium Carbonate Period II	11,933	6486	9,987	33,105	4362	- 37	+1514	+2221	+3531	+1006
Calcium Carbonate Period III	10,793	4628	9,725	31,587	4118	+1103	+3372	+2483	+5049	+1250
Control Period III	12,215	6695	11,157	3,788	4974	- 319	+1305	+1050	+ 848	+ 394

TABLE 6

DAILY MINERAL EXCRETION IN THE URINE BEFORE AND
DURING CALCIUM CARBONATE THERAPY

A.B.C. 125056	M 57	Vol. (cc.)	pH	Cl (mg.)	Ca (mg.)	NH ₄ (mg.)
Before calcium carbonate		2000	5.54	3900	217	3004
		2200	5.59	2816	317	2973
During calcium carbonate*		810	5.81	805	463	1575
		1030	5.80	951	410	2000

*28 gms. daily for 3 days prior to and during the
analyses.

TABLE 7

DAILY MINERAL EXCRETION IN THE URINE BEFORE AND DURING
CALCIUM CARBONATE THERAPY IN A PATIENT
WITH HISTAMINE ACHLORHYDRIA

J. M. 179738	M 58	Vol. (cc.)	pH	Cl (mg.)	Ca (mg.)	NH ₄ (mg.)
Before calcium carbonate		2130	6.52	1210	57	2535
		2325	6.30	991	62	3248
During calcium carbonate*		3252	6.30	693	300	2106
		2940	6.31	1252	221	1441
		2365	6.14	1343	...	3434

*20 gms. daily for 4 days prior to and during analyses.

PART VI. THE ALKALOSIS OF CHLORIDE LOSS

A. Experimental Studies in the Dog

B. Experimental and Clinical Studies in Man

Published in part in Journal of Clinical
Investigation 20: 303, 1941

INTRODUCTION

In the clinical studies, the question arose as to the role of the loss of gastric chloride in the development of alkalosis. It was thought desirable, therefore, to investigate this subject further, experimentally, and studies were made both in the dog and in man.

A. EXPERIMENTAL STUDIES IN THE DOG

METHOD OF STUDY

Chloride deprivation was produced gradually by the intermittent withdrawal of the gastric contents, an effort being made to keep all other conditions as nearly normal as possible. For this purpose two healthy female dogs were operated upon under ether anesthesia. A special gold-plated cannula¹ was introduced into the stomach and was brought through the abdominal wall to the exterior. After recovery from the operation, the dogs were placed on a liberal diet with added vitamins. The chloride content of the food was carefully determined and the intake of salt

¹The gastrostomy cannula employed is similar to that described by Dragstedt (Surg., Gyn., and Obst. 56: 799, 1933). In the quantitative collection of gastric juice intermittently over a period of weeks, the addition of a plunger to Dragstedt's cannula has proved useful. The cannula proper consists of a brass tube with an internal diameter of 1.1 cm. and is 7.5 cm. in length. The circular flange at the proximal end has a diameter of 3.5 cm. Attached to the cap, which screws on the distal end of the cannula, is a closed hollow brass cylinder so constructed in diameter and length that it completely fills the lumen of the cannula. Both the cannula and the plunger are gold-plated. The introduction into the stomach is simple. An incision is made in the anterior surface of the antrum just long enough to permit insertion of the flange. Two purse-string sutures are taken in the stomach around the shaft of the cannula and the omentum is wrapped around the shaft. The distal end of the cannula is brought to the outside through a stab wound in the abdominal wall. There has been no leakage with subsequent excoriation of the skin and no loss of gastric juice in dogs prepared by this method. On withdrawal of the cap and plunger, there is an immediate flow of gastric contents undiluted by materials which usually accumulate in the shaft of a cannula with a simple cap.

was maintained at a low level almost constantly except for one short period during which food with a higher salt content was inadvertently used. The chloride intake in dog 14 (wt. 7.6 kg.) averaged 315 mg. daily excluding seven days when the daily intake approximated 499 mg. The chloride intake in dog 35 (wt. 11.0 kg.) averaged 467 mg. daily except for one week during which the daily amount rose to 746 mg. Both dogs received a liberal allowance of chloride-free water which they drank freely throughout the experiment. In dog 14 the intake averaged 237 cc. daily for most of the experimental period; this amount was increased to 366 cc. daily during the final four weeks. Dog 35 received 331 cc. daily at first. The intake was then increased to 462 cc. and during the last seven days averaged 975 cc. (including 100 cc. of 2½% sodium citrate and 300 cc. 5% glucose in distilled water intravenously).

The weight of the animals was checked every 7 to 14 days. The serum chloride, carbon dioxide, and pH, and the blood urea nitrogen were determined at weekly intervals (1); in addition, renal function in dog 35 was measured by the urea clearance test (2). The urine was collected for two hours in these studies. After a control period of several weeks, the removal of gastric contents was begun. The dogs were trained to stand quietly on a table and the secretion of gastric juice was stimulated with hourly subcutaneous injections of histamine, the average dose ranging from 0.33 to 0.50 mg. in dog 14 and from 0.50 to 1.0 mg. in dog 35. The contents were collected in glass Soxhlet flasks, after removal of the screw-cap plunger from the cannula, for three hours each day. Food and liquids were placed in the cages after each collection. Accurate records were kept of the volume of secretion removed daily; the pH was determined with a Beckman pH meter; the chlorides were measured by the method of Van Slyke and Sendroy (1). It was impossible to prevent the occasional accumulation of saliva in the stomach; regurgitation of bile, however, was infrequent. A histologic study of the kidneys, and other organs, was carried out at the completion of each experiment.

RESULTS

The gastric contents were withdrawn intermittently from dog 14 over a period of 74 days. It will be noted (Fig. 1) that

the serum chloride decreased gradually from an average of 105.5 mM/L to the low value of 46.8 mM/L, a reduction of 56%. The serum carbon dioxide rose to a peak of 56.2 mM/L, and the pH increased to a level of 7.63. The total anion concentration (Cl and HCO_3) decreased from an average of 135 mM/L when the acid-base balance was normal to 103.1 mM/L as the hypochloremia became severe. Despite the severe hypochloremia and alkalosis, the blood urea nitrogen ranged only from 14 to 19.7 mg.%. It will be noted

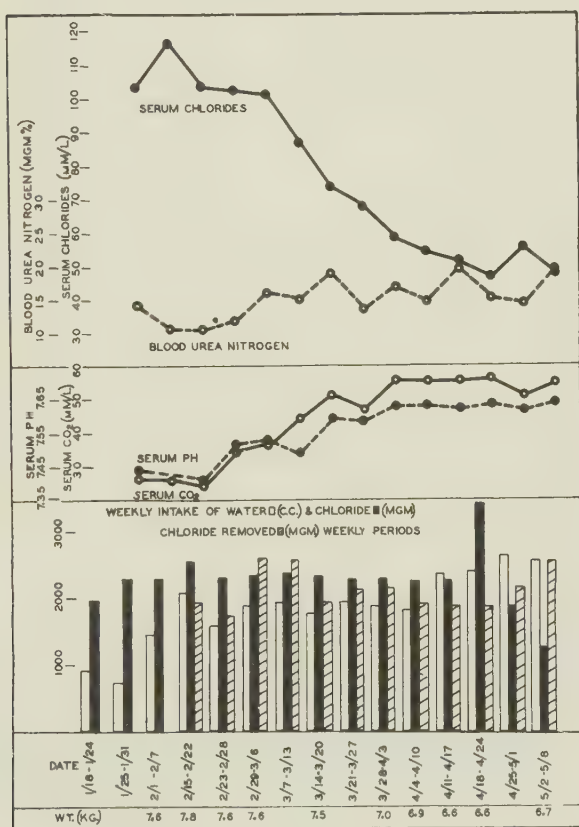


Fig. 1.--The effect of gradual chloride depletion on the acid-base balance and blood urea nitrogen in dog No. 14.

(Table 1, Fig. 2) that the volume and chloride content of the gastric juice decreased moderately while the pH rose slightly. Weight loss amounted to 1.1 kg. or 14% of the body weight and occurred chiefly during the latter stages of the experiment. Weakness gradually increased and on the seventy-fourth day the withdrawal of gastric juice was discontinued. The dog was found dead in its cage several days later. At necropsy, the lungs were congested but there was no evidence of pneumonia. The kidneys showed early post-mortem changes. The glomeruli and tubules were normal on microscopic examination, although considerable protein precipitate was present in the glomerular spaces and in the tubules. Calcium was not found in the kidney, using von Kossa's silver nitrate stain. One parathyroid gland was successfully located and appeared entirely normal on histologic examination.

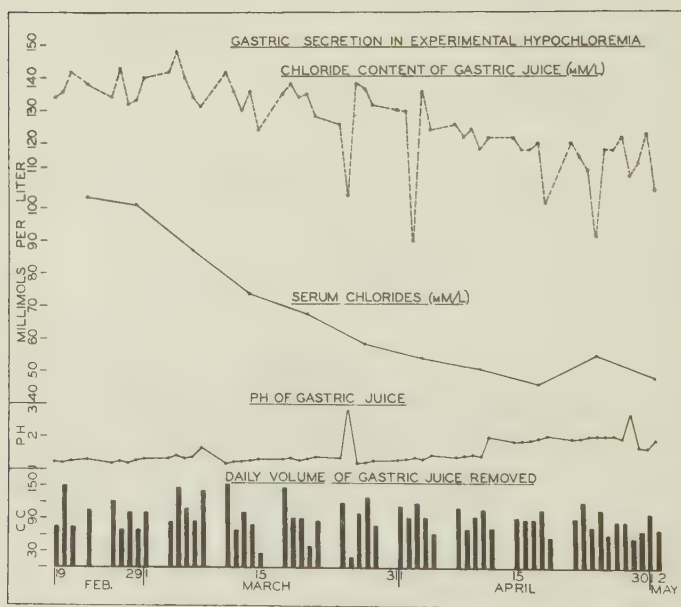


Fig. 2.--Effect of gradual hypochloremia on volume, pH, and chloride content of histamine-stimulated gastric secretion in dog No. 14.

The gastric contents were withdrawn intermittently from dog 35 for 86 days. The serum chloride, carbon dioxide and pH remained normal for 39 days by which time 13,510 mg. of chloride had been removed (Fig. 3). In the following week, the serum chloride decreased appreciably and eventually diminished from an average of 107.3 mM/L to the low level of 38.9 mM/L, a reduction of 64%. The serum carbon dioxide rose to a height of 57.5 mM/L and the pH to a level of 7.72. During the final two days the serum carbon dioxide and pH decreased despite the progressive hypochloremia. The total anion concentration (Cl and HCO_3) diminished from an average of 131 mM/L when the acid-base balance was normal to the very low value of 82.1 mM/L during the final stages of the hypochloremia. The blood urea nitrogen values ranged from 10.9 to 17.1 mg.% when the serum chloride was normal, and from 16.8 to 28.6 mg.% during the hypochloremia. The total blood nitrogen, non-protein nitrogen, and plasma proteins were normal several hours before death, the values being 10.14 gm./L, 0.40 gm./L, and 6.09 gm.% respectively. The urine volumes in dog 35 averaged 1.72 cc. per minute during the control period and 1.46 cc. per minute during chloride deprivation. Urine collections (two-hour periods) were delayed until diuresis occurred. The urea clearances remained normal throughout the experiment, ranging from 68.9 cc. to 41.8 cc. of blood per square meter when the serum chloride was normal, and from 50.9 to 47.2 cc. during the chloropenia, except for one value of 38.7 cc. The average daily volume of gastric juice was unchanged, the pH rose slightly, and the decrease in chloride content was comparatively small (Table 1, Fig. 4). The animal lost 1.5 kg. or 13.5% of his body weight, almost entirely during the last seven days of the experiment. Muscular hyperirritability developed on the eighty-eighth day followed by death several hours later. At necropsy, the glomeruli of the kidney were normal; there was slight focal tubular atrophy with cortical scarring. The lumina of many of the collecting tubules were filled with blue-staining masses which proved to be calcium (Fig. 5).

Excretion of ingested water was delayed in both dogs as the chloride loss was intensified. However, after diuresis appeared, urine volumes during the hypochloremia closely approximated those obtained when the acid-base balance was normal. Direct measurements of the blood sodium were not made in these

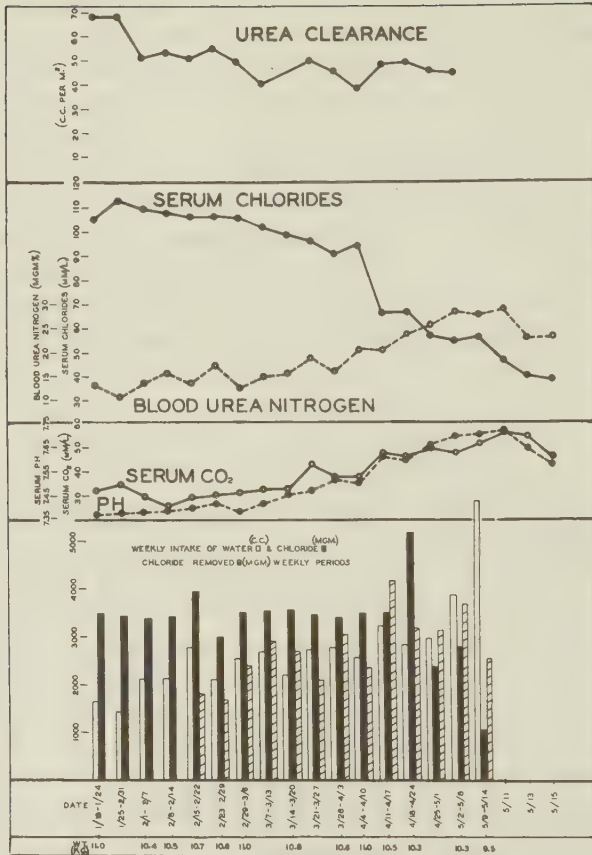


Fig. 3.--The effect of gradual chloride depletion on the acid-base balance, blood urea nitrogen, and urea clearance in dog No. 35.

experiments. However, the fact that the sum of the anions (Cl and HCO_3) was much below normal indicates a decreased concentration of cation, i.e., sodium. Analysis of the skin, skeletal muscle, liver, and kidney in both dogs revealed a markedly reduced chloride content.

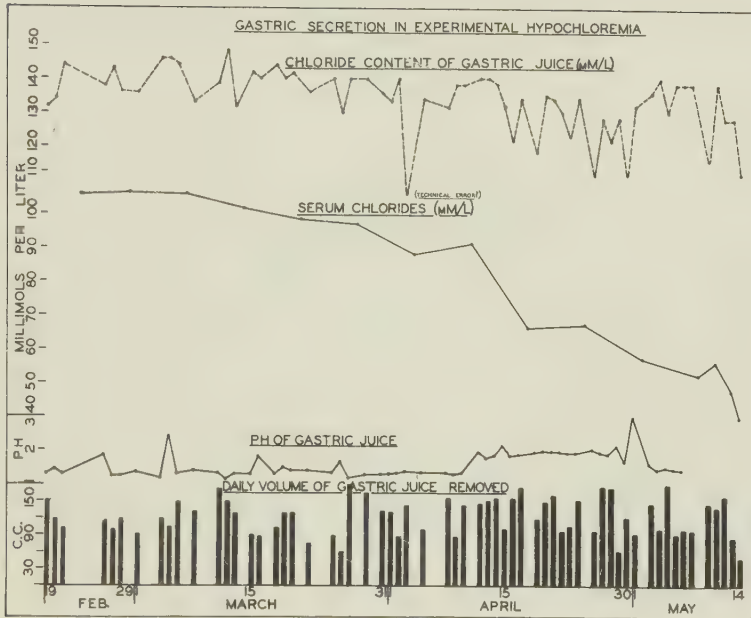


Fig. 4.--Effect of gradual hypochloremia on volume, pH, and chloride content of histamine-stimulated gastric secretion in dog No. 35.

DISCUSSION

Acid-Base Balance

Inasmuch as the gastric juice is derived from water and electrolytes taken from the blood plasma, and inasmuch as the chief electrolyte in gastric juice is chloride, with a small amount of sodium, the continued loss of gastric secretion involves a considerable loss of chloride and a much smaller but significant depletion of sodium (3). The loss of chloride is replaced mainly by a compensatory increase in bicarbonate, and, therefore, does not alter the total electrolyte value at first, whereas loss of base is not replaceable except from the diet, and, moreover, carries with it an equivalent quantity of bicarbonate ion.

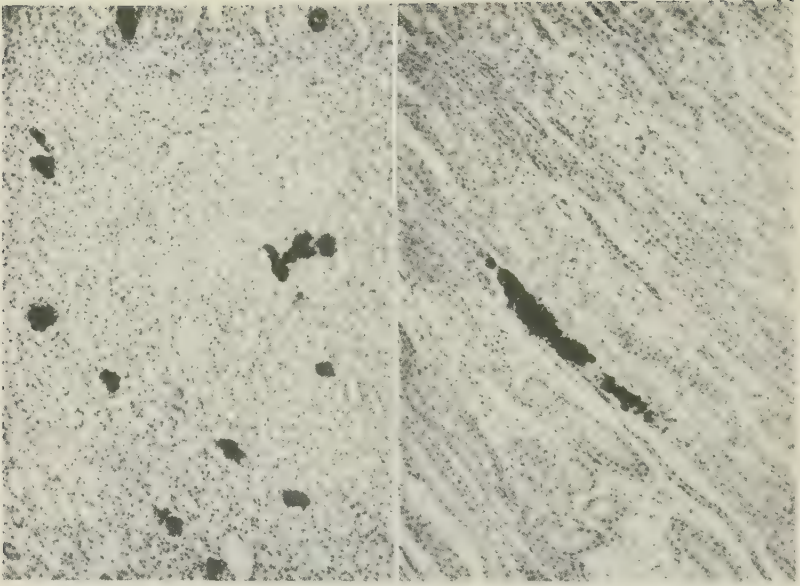


Fig. 5.--Photomicrograph demonstrating presence of calcium precipitate in renal collecting tubules in dog No. 35.

Azotemia and Renal Function

The deficit of base is accompanied by a corresponding loss of extracellular water, leading to a reduction in the volume of extracellular fluid (4). Severe nitrogen retention usually accompanies such acute disturbances (5). Dragstedt and Ellis (6) found, during experimental hypochloremia induced in the dog by the rapid removal of gastric juice, an elevation of the urea nitrogen from 12 to 154 mg. and of the non-protein nitrogen from 27 to 180 mg., when the whole blood chloride was lowered from 300 to 108 mg. Several explanations have been offered to account for the development of azotemia under such circumstances. Some investigators (7) related the retention of nitrogen directly to the hypochloremia and attributed the rise in blood urea to reabsorption of urea through the tubules of the kidney in order to raise the subnormal osmotic pressure of the plasma. Urea, however, is a crystalloid, and even if reabsorbed, would not regulate the os-

motie pressure of the plasma as originally conceived, for it diffuses freely through all the tissues of the body. As McCance (5) points out, nothing can act as an efficient substitute for an extracellular electrolyte unless its distribution is limited to the extracellular fluids. Marked nitrogen retention, furthermore, has been observed frequently in the presence of normal or high levels of plasma chloride (8).

A second cause which has been given for the development of extrarenal azotemia is the increased protein catabolism of dehydration (9). Numerous investigators (10) have shown that deprivation of water alone may accelerate the breakdown of protein. McCance (11) found during acute salt deficiency produced by diet and sweating that with a reduction in the volume of body fluids of from 28 to 38%, the subjects were in negative nitrogen balances. Both in clinical and experimental salt deficiency, the loss of chloride is abrupt and is rapidly followed by a marked loss of body water. The nitrogen retention, therefore, may be explained simply on the basis of excessive protein breakdown associated with anhydremia (12).

The azotemia during hypochloremia has been attributed also to impaired renal function secondary to dehydration (13). This concept is supported by the findings of Landis *et al.* (14), in that the mild elevation of blood urea nitrogen following restriction of sodium chloride was accompanied by a slightly diminished average 24-hour urea clearance. The conventional one-hour clearances were normal. McCance and Widdowson (15) found a decrease of the creatinine, sucrose, inulin, and urea clearances during acute salt deficiency. These decreases were attributed to diminished glomerular filtration and to increased tubular reabsorption of urea. Eventual reduction of the volume of blood plasma by the process of dehydration causes physical changes in the blood, and in the mechanics of its circulation which greatly reduce volume flow through the kidneys, with the result that accuracy of renal function is impaired. These changes include: increased colloidal osmotic pressure; increased blood viscosity, decreased blood volume; a reduction in the number of "active glomeruli"; and a decrease in the rate of circulation. Regardless of the specific mechanisms operative, it is apparent that the basic renal disturbance is not one of primary or secondary renal disease but of impaired renal function secondary to dehydration.

This study indicates that a gradually induced hypochloremia is not necessarily accompanied by severe nitrogen retention. Kerpel-Fronius (9), Ambard and his associates (16), and Hiatt (17) have made similar observations. The decisive factor which determines the extent of azotemia during hypochloremia appears to be the degree and rapidity of dehydration associated with the chloride loss. The extracellular fluid was not measured but presumably was diminished. Evidence for its decrease is to be found in the significant loss of weight sustained by both dogs and also in the established fact that loss of body fluid occurs with a decrease in serum electrolytes (18). Since the animals drank chloride-free water daily and in considerable amounts, it would appear that dehydration did not exist in the sense of deprivation of water, but was present in the sense that loss of body fluid accompanied the loss of electrolytes. However, the dogs apparently were able to make rather satisfactory adjustments to severe changes in the electrolyte balance during most of the experiment. The urea clearances in dog 35 did not differ greatly from the average values reported for the normal dog by other authors (19). The normal urea clearances and the finding of normal nitrogenous constituents in the blood several hours before death are evidence of adequate renal function. The mild elevation of blood urea nitrogen may be considered as indicative of a decrease in renal function too small to be detected by the usual clearances, as suggested by the work of Landis. The explanation of such an assumed impairment of renal function, however, is not easily hypothesized. The urinary volumes were excellent, although we observed, as have other workers, an unexplained delay in water diuresis in these animals.

Gastric Secretion during Hypochloremia

The results of the present investigation are in complete accord with other studies in demonstrating that during periods of marked hypochloremia the gastric mucosa is able to secrete normal amounts of highly acid gastric juice. Dragstedt and Ellis, working on dogs with total gastric pouches, found that the gastric glands continued to secrete in spite of a plasma chloride level lower than one-third of normal; the volume of secretion, however, was reduced and its acidity lessened. Lim and Ni (20) observed a

continued secretion in dogs despite dehydration and a loss of one-half of the total body chloride. Katsch and Mellinghoff (21) and Mellinghoff and Heuschert (22) withdrew gastric juice from patients for ten hours each day for three to five days, removing up to 33 gms. of sodium chloride, and produced an average fall in the whole blood chloride of 51 mg. per 100 cc. The gastric secretion showed a 20% reduction in volume without significant change in the chloride content. The response to histamine was as good, or almost as good, on the last day of treatment as it had been on the first. McCance found that salt deficiency produced by diet and sweating tended to reduce the concentration of acid and chloride in gastric juice but that individuals varied widely in their response. Soley, Lagen, and Lockhart (23) examined three healthy men over a period of one week on a salt-deficient diet, an increased output of salt being obtained by frequent periods of sweating. They found no significant change in the free acidity of the gastric juice under these conditions. The degree of salt deficiency, however, was very slight. Nicol and Lyall (24) studied a group of patients with peptic ulcer in whom hypochloremia had been induced by vomiting, and concluded that the gastric mucosa could still secrete normal amounts of hydrochloric acid. The blood chloride in one patient had decreased to 60 mM/L. Hiatt (17) has recently found that in dogs with chloride levels below 65% of normal, the volume and total acidity of the histamine-stimulated gastric secretion is decreased. The chloride secretory function of the gastric glands differs from the chloride excretory function of the skin, choroid plexus, and kidney in that chloride excretion diminishes or ceases completely in the presence of a severe hypochloremia.

Anatomic Changes in the Kidney

The calcium precipitate observed in the renal collecting tubules in dog 35 is of considerable interest. This condition was described originally by Nazari (25) in 1904 in two patients with prolonged vomiting secondary to pyloric stenosis. Many similar reports (26) subsequently appeared, but the mechanism of the condition remains incompletely understood. Calcium salts are not infrequently deposited in necrotic kidney cells. Martz and others believe that the secretion of an acid urine during severe alkalosis makes the cell fluids of the kidney even more alkaline and

thereby favors the precipitation of calcium. Hatano (27) was able to prevent this complication during hypochloremia by the intravenous injection of sodium chloride which tended to correct the acid-base balance. The use of sodium bicarbonate proved ineffective. Gümöri and his co-workers (9) have frequently observed fat degeneration with necrosis and calcification in the kidneys of patients dying of "hypochloremic uremia." Since the kidneys in the present experiment were normal, the calcium precipitate may be the result of an abnormal physical chemical state in the urine, with a precipitation of calcium phosphate and calcium carbonate.

CONCLUSIONS

1. Severe alkalosis may be induced in the dog by the gradual withdrawal of gastric secretion.
2. The acid-base disturbance is not necessarily accompanied by severe or, indeed, even marked nitrogen retention.
3. Such an alkalosis apparently does not produce impairment of renal function detectable by the urea clearance test, or renal injury detectable by histologic examination of the kidney.
4. The secretion of hydrochloric acid by the gastric mucosa is relatively uninfluenced by a profound hypochloremia.

B. EXPERIMENTAL AND CLINICAL STUDIES IN MAN

INTRODUCTION

The preceding study demonstrated that a severe hypochloremia and alkalosis could be induced gradually in the dog by means of continued loss of chloride without the development of a marked azotemia or detectable renal injury. The present investigation was undertaken to determine whether or not the same situation could be induced in man.

METHOD OF STUDY

I. Acute Hypochloremia

The relationship of chloride loss to azotemia was first

studied in two individuals (Cases R. S. MacK. and B. G.) in whom the hypochloremia was produced rapidly.

II. Subacute Hypochloremia

Chloride deprivation then was produced more slowly by Wangensteen aspiration of the gastric contents for varying lengths of time in two adult men (Cases M. S. and W. L.) with pyloric obstruction secondary to duodenal ulcer.

The patients received no food or fluid by mouth during the period of chloride withdrawal; 3000 to 4500 cc. of 5% glucose in distilled water were administered intravenously each day. The serum chloride, carbon dioxide, pH, and blood urea nitrogen were measured frequently (1). Renal function in case M. S. was determined by the urea clearance test. Measurements were made also of the serum calcium (28), phosphorus (29), and potassium (30). The cell volume was determined frequently by hematocrit readings. The plasma proteins were determined by the Hanna-Campbell method (31), a modified macro-Kjeldahl technique being employed for the nitrogen analysis; 4% boric acid was used to absorb the ammonia released. The blood sodium was measured by a modification of the Butler-Tuthill method (32); the phosphate of the serum was removed by ignition with ferric sulfate and the sodium determined on an aliquot from which the insoluble iron salt had been removed by centrifugation. The urinary sodium was determined in case M. S. by the same technique as used for the serum sodium modified as to the volume used; ferric salt was added in amounts sufficient to prevent interference by phosphates. The total base was measured by a modification of the Stadie-Ross technique (33); the serum was ashed as for the sodium analysis; the ash was taken up in 45 cc. of water, the bases precipitated with benzidine hydrochloride, and the difference between the titrations of the acidity of this filtrate and that of the original reagents used as a measure of the total base.

The patients' body weights were checked frequently. The fluid intake and output were recorded daily. The pH of the urine was determined with a Beckman pH meter; the chloride content of the urine was measured by the Van Slyke-Sendroy method; and the ammonia plus ammonia salts determined by the technique of Henriques and Sørensen (34). The volume, pH, and chloride content of the aspirated gastric secretions were measured similarly.

Aspiration of the stomach was discontinued after a severe but safely obtainable state of chloride depletion had been achieved. The body chloride was then replaced gradually in case M. S. over a period of 26 days by the addition of increasing amounts of salt. The body chloride was replaced more rapidly in case W. L. (within six days) by the parenteral administration of saline solution.

III. Hypochloremia Incidental to Ulcer Therapy

The problem was studied further in ten additional patients with alkalosis and chloropenia complicating the treatment of peptic ulcer. While two factors were operative in this latter group, i.e., chloride loss and alkali ingestion, these cases are included because of the absence of nitrogen retention and because the evidence reported in previous sections indicates that the major, indeed, if not the only factor, in the acid-base disturbance, is the hypochloremia.

RESULTS

I. Acute Hypochloremia

Case 1.--R. S. MacK. (Unit no. 85594), a 43-year-old steamfitter, entered the hospital because of recurrent pyloric obstruction secondary to a duodenal ulcer. Two thousand to three thousand cc. of 5% glucose in normal saline were injected intravenously daily. Twenty-seven hundred and 1850 cc. of highly acid gastric contents were removed by Wangensteen suction on the twenty-fourth and twenty-fifth hospital days. The fluid intake at this time consisted of 3000 cc. of 5% glucose in distilled water intravenously each day. After 36 hours of continuous aspiration, the patient suddenly became extremely weak, cold, and cyanotic. The pulse rate rose to 115 and the blood pressure, originally 108/70, decreased to between 50 and 80 systolic. The patient became confused and irrational, and he lapsed into a coma which persisted for two minutes. Five per cent saline solution was administered intravenously and after 150 cc. had been introduced, the patient's condition rapidly improved. No studies were made of the acid-base balance during the period of circulatory collapse. However, since the serum chloride 12 hours previously

had been 79 mM/L and the withdrawal of gastric content had been continued, it is apparent that the serum chloride was probably below this level. The blood urea nitrogen 24 hours previously had been 25.1 mg.%.

Case 2.--B. G.¹ (Unit no. 119566), a 42-year-old housewife, had been treated at the University Clinics for six years for a duodenal ulcer with obstruction. Persistent nausea and vomiting had been present for one month prior to hospitalization. The gastric contents were aspirated from the third to the seventh hospital days. The amounts removed daily varied from 400 to 900 cc.; the pH of the aspirates ranged from 2.01 to 2.97.

The fluid intake during this period consisted of 3000 cc. 5% glucose in distilled water given intravenously. The serum chloride decreased to 56.7 mM/L after five days of gastric aspiration. The serum CO₂ rose to 41.3 mM/L and the pH to 7.67. The maximum blood urea nitrogen was 18.6 mg.%, obtained on the day of the lowest chloride. The blood urea nitrogen varied usually from 6.1 to 16.7 mg.%. The daily volume of urine ranged from 940 to 3200 cc. with an average of 1705 cc. The chloride content of the urine was very low.

The patient became very weak, and her blood pressure, which on admission had been 150/90, decreased to between 90 and 110 systolic and between 68 and 74 diastolic. On the fifth day of gastric aspiration the blood pressure fell to 72/50 and since the patient appeared to be in mild shock, gastric aspiration was discontinued. On this same day, the patient fell out of bed in a tonic convulsion which lasted several minutes. Recovery occurred promptly after the intravenous administration of 1500 cc. of 5% glucose in normal saline. The serum calcium was later found to be somewhat decreased. This finding is of interest in connection with the work of Yannet (36) demonstrating a reduction in the average calcium concentration during experimental alkalosis induced by sodium bicarbonate. Sodium chloride was given by mouth and the patient gradually recovered, although her blood pressure remained low for several days.

Comment.--The acute collapse with convulsions and coma, and the marked drop in blood pressure occurring in these two cases

¹This patient died in alkalosis after prolonged vomiting during a subsequent hospitalization; the necropsy findings are described on pp. 155 ff.

simulate closely the clinical manifestations of severe adrenal insufficiency. The immediate response to saline therapy is an additional point of resemblance. McCance (5) has reported similar observations. There are certain differences in electrolyte structure, however, between the two conditions. Thus, the low blood bicarbonate and the increased serum calcium, phosphorus, and potassium noted frequently during the crises of Addison's disease were not observed in the present experiments. Loeb (37) has pointed out that Addison's disease may resemble clinically other conditions in which the loss of inorganic base plays an important role.

II. Subacute Hypochloremia

Case 1.--M. S. (Unit no. 204878) (Figs. 6 and 7), a 38-year-old salesman had taken alkalis intermittently for five years for the relief of symptoms from a stenosing duodenal ulcer. He had been vomiting for five days prior to hospitalization. Five per cent glucose in both normal saline and distilled water was administered intravenously during the first four days. Continuous Wangensteen aspiration of the gastric contents was begun on the fifth day and continued for 96 hours. The gastric contents removed each day were acid, the pH ranging from 1.84 to 2.70; the amounts varied daily from 1100 to 3090 cc. Wangensteen suction was then limited to a period of ten hours daily, the amounts withdrawn ranging from 440 to 1200 cc. The intravenous intake of fluid during the period of gastric aspiration consisted of 5% glucose in distilled water, except for 1500 cc. normal saline given on the twelfth day. This represented the only chloride (8.1 gms.) taken by the patient during the interval from the fourth to the sixteenth hospital days. The salt intake was then increased very gradually until discharge from the hospital on the thirty-ninth day, at which time the patient was receiving 3.7 gms. of chloride daily. This amount was increased to 5.3 gms. daily one week later and the chloride intake was maintained at this level until the experiment had been concluded.

The lowest serum chloride of 53.8 mM/L was obtained on the eleventh day. The serum CO_2 increased to 43.1 mM/L and the pH to 7.70. The maximum blood urea nitrogen of 30 mg.% was obtained at a time when the serum chloride measured 63.6 mM/L; the values ranged usually from 14.2 to 19.6 mg.%. The blood sodium

decreased to 115.2 m.Eq./L and the total base to 133.3 m.Eq./L. The serum calcium and potassium were normal. The urea clearance was not lowered significantly. The patient's body weight decreased from 73.4 to 63 Kg.; the presence of dehydration was further indicated by the increased hematocrit readings and the high plasma protein values.

The acid-base balance, hematocrit, and plasma proteins gradually returned to normal during the period of chloride replacement. The blood urea nitrogen ranged from 8.1 to 14.3 mg.%. At the conclusion of the experiment, the patient's body weight

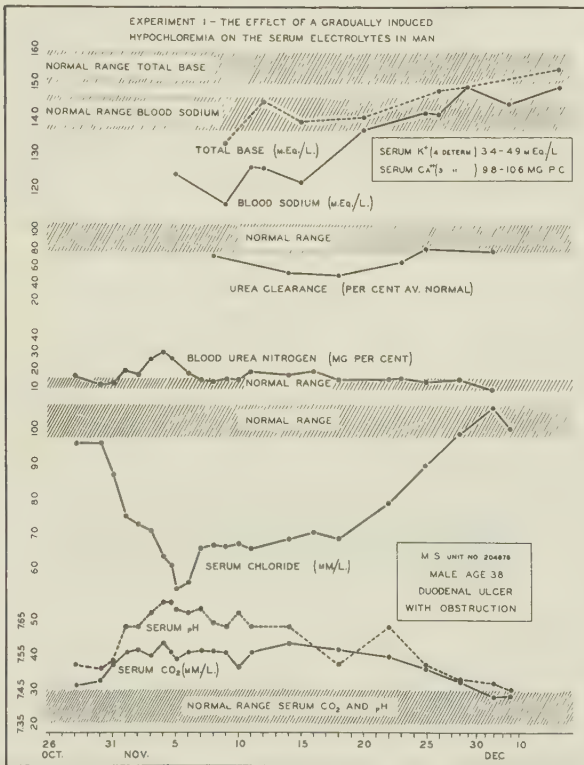


Fig. 6.--The effect of a gradually induced hyponatremia on the serum electrolytes in man. Case M. S. (Experiment 1).

had returned to its original level. The daily volume of urine varied from 775 to 1920 cc., usually exceeding 1000 cc.; the pH ranged from 5.9 to 6.85. Its chloride content was markedly reduced, with daily values of between 36 and 72 mg.; no chloride was found in the urine on four days. Sodium excretion paralleled the values found for chloride ion and ranged from 54 to 438 mg. in contrast to a 24-hour output of 4771 mg. when the acid-base balance was normal. Ammonia excretion in the urine also was diminished.

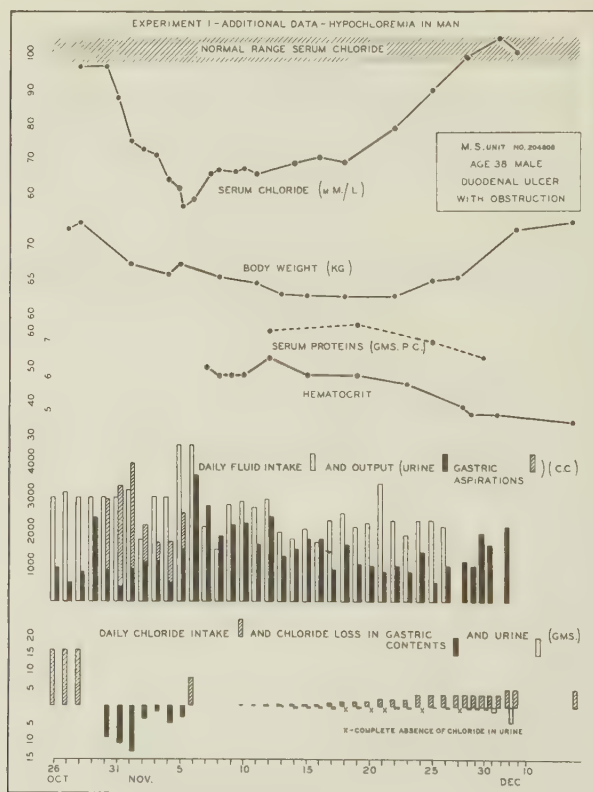


Fig. 7.--Hypochloremia in man. Additional data in Case M. S.

A histamine test performed on the nineteenth day (serum chloride between 65.5 and 68.8 mM/L) revealed normal gastric secretion; the pH of the various samples of gastric juice ranged from 1.31 to 1.71. An examination of the spinal fluid on the twenty-fifth day (serum chloride between 68.5 and 78.8 mM/L) revealed a clear fluid under normal pressure. The chloride measured 100.4 mM/L and the total base 141.5 mM/L (both values moderately reduced). The calcium was 4.8 mg.% and the urea nitrogen 16.7 mg.% (both values normal).

The patient was very weak and listless during the period of chloride depletion. He had no appetite and complained of a loss of the sense of taste. Mild muscular twitchings appeared on the twelfth day (serum chloride 53.8 mM/L) at which time the patient received the 1500 cc. normal saline intravenously noted above. The blood pressure, originally 130/95, decreased during the period of hypochloremia; the systolic ranged from 90 to 110 and the diastolic from 60 to 72. The blood pressure at the completion of the experiment was 126/84. The patient's clinical course during the period of gradual chloride replacement was characterized by a steady gain in strength and improvement in appetite.

Case 2.--W. L. (Unit no. 254018) (Figs. 8 and 9), a 39-year-old male had experienced ulcer symptoms for several years. He entered the hospital because of a recent massive hemorrhage and marked pyloric obstruction. Therapy consisted of Wangensteen aspiration of the gastric contents, three blood transfusions, and, for the first week, 1500 to 3000 cc. of 5% glucose in normal saline each day. On the eighth day and for the next five days, the patient received 5% glucose in distilled water. An average of 1860 cc. of gastric contents were aspirated daily; the pH of the aspirates ranged from 1.94 to 2.58. Wangensteen suction then was discontinued; the patient, however, vomited large amounts of gastric contents on several occasions. Saline therapy was resumed on the fourteenth hospital day and the patient was given from 3000 to 4500 cc. of 5% glucose in normal saline and distilled water daily. Aspiration of the stomach was resumed on the twentieth day but the electrolyte loss now was replaced by the use of parenteral fluids.

The serum chloride decreased to 58.9 mM/L. The serum CO₂ increased to 51 mM/L, and the pH to 7.69. The maximum blood urea nitrogen was 23.1 mg.%, with the values ranging usually from 13.1

to 21.2 mg.%. The lowest blood sodium was 129.2 mEq./L, obtained on the day of the lowest serum chloride. The serum calcium, phosphorus, and potassium were normal. Adequate urea clearance studies were not obtained in this case. The patient's body weight decreased from 53.5 to 50 Kg. and the plasma protein and hematocrit values were elevated. The volume of urine varied from 660 to 4000 cc. daily, usually approximating 3000 cc.; the pH ranged from 6.41 to 7.48. The chloride content of the urine was markedly reduced; the 24-hour values varied from 48 to 1045 mg.

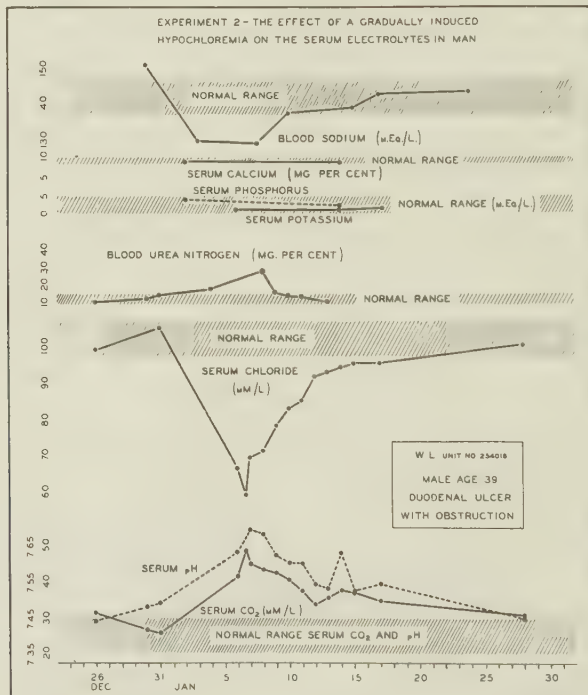


Fig. 8.--The effect of a gradually induced hyponatremia on the serum electrolytes in man. Case W. L. (Experiment 2).

The patient gradually became very weak and listless during the period of chloride depletion. His blood pressure, originally 125/92, decreased slightly; the systolic ranged from 90 to 116 and the diastolic from 68 to 90. These manifestations dis-

appeared rapidly, however, as the acid-base balance was restored.

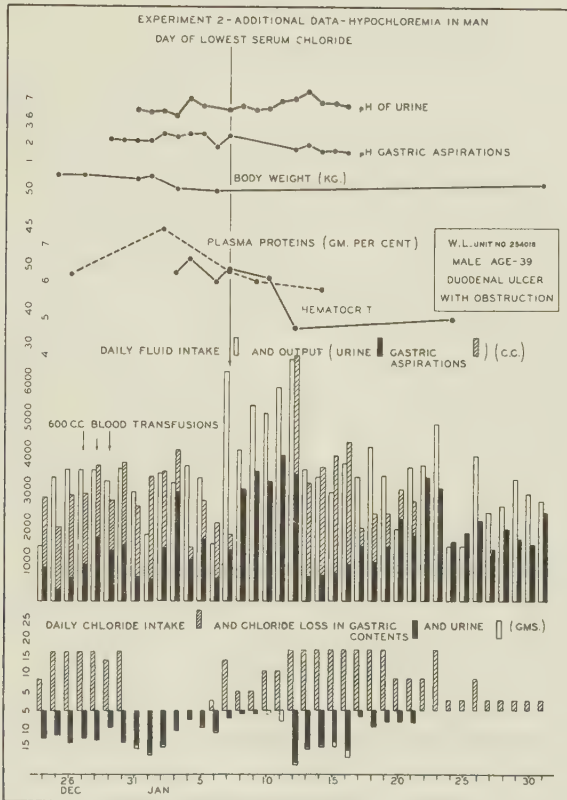


Fig. 9.--Hypochloremia in man. Additional data in Case W. L.

Comment.--The maximum blood urea nitrogen values of 30.0 and 23.3 mg.% noted in these two cases are in sharp contrast to the severe nitrogen retention observed by other workers in patients with hypochloremia and alkalosis secondary to pyloric obstruction, or during experimental salt deficiency produced by diet and sweating (15). Dehydration was present in both patients as evidenced by the significant weight loss and the high hematocrit and plasma protein values. The low blood sodium likewise indicates that a marked decrease in the volume of extracellular fluid had occurred (4).

Since large quantities of glucose in distilled water were administered daily, it would appear that, as in the dog experiments, dehydration did not exist in the sense of deprivation of water but was present in the sense that fluid could not be retained in the body due to the marked depletion of electrolytes. The volume of urine excreted by both patients during the period of hypochloremia was large; the daily output averaged 1340 cc. in case M. S. and 1317 cc. in case W. L. The urea clearance in case M. S. was not altered significantly, and the absence of a marked elevation of the blood urea nitrogen is further evidence of satisfactory renal function. Despite the severe chloropenia, the pH and chloride content of the gastric aspirations were reduced only slightly; and the pH values of the histamine-stimulated gastric juice in case M. S. were as low as one finds in the histamine-stimulated gastric secretion of individuals with a normal acid-base balance. The decrease in the spinal fluid chloride and total base noted is of interest and, of course, to be expected; McCance (11) and Agar and MacPherson (35) have reported similar findings.

III. Hypochloremia Incidental to Ulcer Therapy

In Table 2 are recorded the acid-base balance and other data in ten patients with alkalosis and hypochloremia complicating the antacid treatment of peptic ulcer. Large amounts of gastric content had been aspirated in eight of this group. In no instance was there any significant azotemia. The maximum blood urea nitrogen of 23.3 mg.% was noted in case H. B. at a time when the serum chloride measured 90.4 mM/L. The blood urea nitrogen in case J. S., with a serum chloride of 65.9 mM/L, was only 18.4 mg.%, and in case J. C., with a serum chloride of 67.6 mM/L, only 14.6 mg.%; alkalosis had been present in both individuals on admission to the hospital. Hypochloremia apparently had occurred gradually in all ten patients.

GENERAL DISCUSSION

This study confirms the results of the previous experiments, and demonstrates that, in man, as well as in the dog, a severe hypochloremia is not necessarily accompanied by azotemia. The important factors which determine the extent of urea nitrogen elevation during hypochloremia apparently are the speed with

which the chloride loss is induced, and the degree and rapidity of the dehydration associated with the chloropenia. An abrupt depletion of chloride is associated with an equally abrupt and marked loss of sodium and, therefore, of body water. Loss of fluid decreases the circulating blood volume which, by reducing the venous return to the heart, presumably lowers the cardiac output. This course of events, as noted above, may actually lead to peripheral circulatory failure. The blood flow through the kidney and the effective glomerular filtration pressure consequently are lowered, both processes resulting in impairment of renal function. The severe nitrogen retention and decreased renal function noted under these conditions by other workers evidently represent an impairment of renal circulation rather than intrinsic renal disease. The absence of azotemia during hypochloremia in the present experiments may be attributed to two factors, (a) the gradual deprivation of chloride allowing the patients to make fairly satisfactory adjustments to the severe electrolyte changes, and (b) the daily administration of large quantities of water which prevented increased protein catabolism, tended to "wash out" the urea nitrogen, and apparently maintained an adequate blood flow through the kidney.

CONCLUSIONS

1. Severe alkalosis without marked nitrogen retention may be induced in man by the gradual withdrawal of gastric secretion.

2. Such a hypochloremia and alkalosis is not associated with decreased renal function, as measured by the urea clearance test, when adequate quantities of fluid are administered daily.

3. Gastric secretion in man is not altered significantly by severe hypochloremia.

4. The clinical syndrome of acute hypochloremia in man may simulate the acute adrenal insufficiency of Addison's disease.

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TABLE 1
GASTRIC SECRETION DURING HYPOCHLOREMIA

	Gastric Juice (Daily Values)		
	Volume (cc.)	pH	Chloride (mM/L)
Dog 14:			
a. Period of normal blood chloride (103.8-101.2 mM/L)	70-150 average 99	1.20-1.43 average 1.30	132-148 average 138
b. Severe hypochloremia (55.2-46.8 mM/L)	56-124 average 84	1.40-2.70 average 1.87	92-126 average 117
Dog 35:			
a. Period of normal blood chloride (108.4-98.4 mM/L)	87-170 average 121	1.18-2.41 average 1.43	132-148 average 140
b. Severe hypochloremia (56.4-38.9 mM/L)	46-159 average 123	1.45-1.65 average 1.51	112-140 average 131

TABLE 2
HYPOCHLOREMIA WITHOUT AZOTEMIA DURING ALKALOSIS
(10 PATIENTS)

Case Sex Age	Acid-Base Balance					Day of Treatment	Gastric Aspiration		Therapy
	Serum Cl (mM/L)	Serum CO ₂ (mM/L)	pH	B.U.N. (mg.%)	Urea Clear- ance (% Avg. Normal)		Avg. Daily Amt. (cc.)	No. Days	
J. S. 264531 M 26	65.9 92.1 92.2	38.0 32.0 35.1	7.52 7.47 7.56	18.4 ... 16.9	90 .. 110	2nd 3rd 5th	622	4	Calcium carbonate-- parenteral fluids-- gastroenterostomy on 8th day.
J. C. 185870 M 29	79.0 67.6 85.2	38.6 38.2 32.4	7.62 7.63 7.50	21.2 14.6 8.8	113 200 91	4th 7th ...	393	11	Sippy powders--NaCl (4-6 gms.) started on 6th day.
D. H. 112315 M 45	98.4 80.4 92.8	26.3 36.9 35.2	7.47 7.62 7.47	 10.4 7.9	85	3rd 11th 15th	217	16	Calcium carbonate-- NaCl (5 gms.) start- ed on 14th day.
J. K. 198439 F 55	90.0 86.2 89.2 95.0	29.9 35.0 34.9 34.4	7.39 7.46 7.50 7.47	15.0 9.1 13.7 15.2	41 67 53 63	4th 12th 16th 19th	207	20	Calcium carbonate-- no NaCl.
T. S. 212524 M 49	94.8 81.8 84.8 97.6 99.0	32.8 ... 36.4 31.5 28.8	7.48 7.54 7.49 7.47 7.48	14.5 19.6 15.2 10.4 8.1		6th 12th 18th 29th 33rd	148	16	Calcium carbonate-- no NaCl.

TABLE 2--Continued

Case Sex Age	Acid-Base Balance					Day of Treatment	Gastric Aspiration		Therapy
	Serum Cl (mM/L)	Serum CO ₂ (mM/L)	pH	B.U.N. (mg.%)	Urea Clearance (% Avg. Normal)		Avg. Daily Amt. (cc.)	No. Days	
F. W. 194370 M 43	96.7 82.8 82.6 98.8 96.6	31.7 37.3 37.5 29.5 31.2	7.56 7.55 7.53 7.38 7.44	12.9 12.4 11.2 11.4	143 ... 93 200 ...	2nd 9th 14th 18th 22nd	177	17	Sippy powders NH ₄ Cl (4-6 gms.) 15th to 22nd day.
W. B. 211777 M 51	... 80.6 85.6 98.1 96.8 97.2 ...	31.8 47.4 41.1 28.0 32.4 34.2 ...	7.48 7.73 7.62 7.49 7.49 7.45	18.7 20.6 18.7 8.8 16.9 18.3 15.3	96 128 54 69 148	7th 13th 16th 28th 40th 47th 1 yr. later	354	43	Calcium carbonate-- NaCl (10 gms.) 8th to 22nd day--various alkalis from 25th to 38th days--calcium carbonate then re- sumed.
H. B. 225751 M 49	90.4 83.0 97.0 101.8 ...	30.6 39.4 35.0 31.0 ...	7.50 7.62 7.47 7.47	23.2 18.7 15.7 11.7 12.0	 85 76 102	4th 9th 13th 17th 4 mo. later	356	17	Calcium carbonate-- NaCl started on 10th day--200 cc. 5% saline intrav. on 10th day.
S. S. 101209 M 37	84.3 ... 95.2 100.2 ...	42.9 30.8 36.0 32.9 ...	7.71 7.51 7.53 7.50	17.3 15.0 11.1	83 112	15th 18th 22nd 24th 1 wk. later	85	20	Sippy powders--NH ₄ Cl (2-6 gms.) from 16th to 20th days.
A. G. 232838 M 52	96.0 89.4 87.8 87.4 91.9	31.1 34.4 35.6 36.7 35.1	7.54 7.47 7.48 7.49 7.52	11.7 ... 22.4 14.2 11.7	 80	2nd 4th 8th 10th 13th	100	15	Calcium carbonate-- NaCl (3 gms.) start- ed on 13th day.

PART VII. THE MORPHOLOGY OF THE KIDNEY FOLLOWING
THE ADMINISTRATION OF ALKALI

A. Experimental Studies in the Dog

B. The Effect of Prolonged Alkali Therapy
and of Alkalosis on the Structure
of the Human Kidney:
Autopsy Observations

Section A published in the Archives of Pathology
32: 76, 1941

INTRODUCTION

In the clinical studies of alkalosis described in preceding sections of this thesis, evidence was presented to indicate that, although the urea clearance frequently diminished during alkalosis, renal function invariably returned to its original level when the acid-base balance was restored. It was further shown that the prolonged ingestion of alkali likewise did not permanently lower renal function. On the basis of these observations, it did not appear likely that either alkalosis or prolonged alkali therapy produced irreversible anatomic renal injury. To secure more direct information on this problem, a histologic study of the kidney was undertaken (A) in dogs before and after the administration of massive doses of sodium bicarbonate and (B) in patients who had received large amounts of alkali and who had died either in alkalosis or of other complications.

REVIEW OF LITERATURE

Various investigators have attempted to clarify this problem by studying the effect on the kidney of the experimental animal. Fischer (1) reported albumin, casts, and red blood cells in the urine of rabbits given large amounts of tenth-normal sodium hydroxide and twice-molar sodium chloride. No histologic studies of the kidney are mentioned. Similar results were obtained with acids, urea, pyridine, and certain amines. Nuzum and co-workers (2) kept rabbits on a diet of ground soy beans (protein content, 36%) for two years. The non-protein and urea nitrogen of the blood remained normal, and there was no evidence of renal damage. The authors' claim that persistent mild alkalosis injures the kidney is not supported by the data presented. Addis, MacKay, and MacKay (3) fed 24 albino rats a diet containing 4% sodium bicarbonate (in man, equivalent to 2,560 cc. of tenth-normal sodium hydroxide) for almost one year. Twenty-four of the 72 urine specimens contained large amounts of blood. In seven rats hydronephrosis developed in one or both kidneys, but in none was the condi-

tion so far advanced as to have produced appreciable renal atrophy. The blood urea nitrogen was normal, and there were no apparent microscopic differences between the kidneys of the control, acid, and alkaline rats. Kellert (4) injected 12 cc. amounts of a 5% sodium bicarbonate solution intravenously in normal rabbits and in rabbits in which renal damage had been induced previously with 0.025 gm. of potassium chromate, 10 cc. of 1:1,000 mercurous chloride, and 0.002 gm. of uranium nitrate. No anatomic evidence was obtained to indicate that sodium bicarbonate in the quantities used was injurious to the kidney. Suzuki (5) fed rabbits a diet of soy bean husks and also injected 5% pure sodium bicarbonate in distilled water intravenously and intraperitoneally. No unusual pathologic changes were noted. The kidneys were hyperemic; on microscopic examination, the epithelial cells were slightly turbid, and there were infrequent hemorrhages in Bowman's capsule. Hoag and his associates (6) injected therapeutic doses of sodium bicarbonate both subcutaneously and intravenously in a series of 47 animals. No significant anatomic changes were noted in the kidney.

Few studies have appeared in the literature describing the effects of alkali therapy and alkalosis complicating antacid treatment on the structure of the human kidney. Hardt and Rivers (7) reported the case of a 66-year-old man who had taken sodium bicarbonate intermittently for 15 years for the relief of ulcer distress. After 15 days of intensive alkali therapy in the hospital, the patient became stuporous and subsequently died despite the use of saline infusions. The plasma CO_2 had measured 44.9 and 50.4 mM/L, the blood urea nitrogen 134 and 212 mg.%, and the blood creatinine 4.3 mg.%. Necropsy revealed a duodenal ulcer, bilateral bronchopneumonia, and generalized arteriosclerosis. Microscopic examination of the kidney disclosed a focal and diffuse interstitial lymphocytic infiltration. Some glomeruli were sclerosed, while others were completely hyalinized; most of the capsules were thickened. The arteries and arterioles were sclerosed.

Cooke (8) reported the case of a 46-year-old man who had taken alkalis for one year. The patient had been vomiting for five weeks, and he was admitted in a semicomatose condition. The serum CO_2 decreased from 56.2 to 31.8 mM/L, and the plasma sodium chloride rose from 353 to 546 mg.% after the administration of

saline. The blood urea nitrogen increased, however, from 165 to 252 mg.%, and the patient died within several days. The kidneys were large and smooth, and engorged with blood. The microscopic changes were interpreted as indicative of a "chronic interstitial nephritis" with a terminal acute nephritis.

Oakley (9) described the anatomic findings in two patients dying in alkalosis after alkali therapy: (1) A 63-year-old male with a duodenal ulcer had been treated with an alkali mixture consisting of magnesium carbonate, sodium bicarbonate, and bismuth oxycarbonate. The patient had received 90 gms. of sodium bicarbonate in four days at which time he became irrational and comatose; he died four days later. The blood urea nitrogen had measured 140 mg.%. The kidneys were normal grossly and the only microscopic findings recorded were swelling and focal fatty degeneration of the tubular epithelium. (2) A 64-year-old man, treated similarly, had received 541 gms. of sodium bicarbonate in 11 days. Symptoms of alkalosis appeared on the eleventh day and the patient died three days later. The blood urea nitrogen 24 hours before death was 250 mg.%; the urine was reported as normal. Microscopic study of the kidneys revealed only a slight amount of fibrosis, occasional arteriosclerotic changes, and a few, small, calcareous deposits.

A. EXPERIMENTAL STUDIES IN THE DOG

METHOD OF STUDY

Thirteen healthy dogs of various body weights were selected for the experiments. One kidney was removed from each animal for control microscopic study. Thus the experiments were carried out in dogs with only one kidney, and therefore constituted a more rigid test of the action of the alkali than was the case in previous studies. After operation the animals were placed on the usual stock diet; the fluid intake was not restricted. Four dogs (100, 30, 50, and 99) did not receive alkali and were killed (by intracardiac injection of air) after periods of 58, 179, 180, and 365 days, respectively, to determine the effect of increased compensatory activity alone on the remaining kidney. This group, therefore, served as a further control for the entire series. Nine dogs received sodium bicarbonate in daily amounts

which were gradually increased from 5 gms. to 60 gms. The smaller quantities of alkali were mixed with the food, while the larger ones were introduced via the stomach tube. Five dogs of this second group (47, 42, 88, 80, and 58) were given sodium bicarbonate by mouth for periods of only 30 to 114 days. The remaining four dogs (94, 66, 46, and 33) received sodium bicarbonate orally each day and intravenously each week for periods of 125 to 261 days. Dog 33 received the enormous quantity of 11,220 gms. of sodium bicarbonate orally in 261 days and 21 intravenous injections totaling 381 gms., or 11,601 gms. in all. The intravenous solution, consisting of 5% sodium bicarbonate in distilled water, was warmed to body temperature and injected at the rate of 5 cc. per minute. Each dog gained weight during the experiment, the increases ranging from 2 to 4 kg. The occurrence of convulsions during alkalosis usually indicated an irreversible acid-base disturbance, unaffected by intravenous administration of saline solution and resulting in death. All the animals except dogs 42 and 88 died in acute alkalosis. Autopsy was performed soon after death. The tissues were placed in Zenker-formaldehyde solution¹ and then were stained, after the usual preparation, by the so-called regressive hematoxylin and eosin stain.

RESULTS

Control Group

No significant renal changes were observed after unilateral nephrectomy in the dogs not given sodium carbonate, as may be seen from the following analysis:

Dog 11 (wt. 12 kg.).--The control kidney (wt. 34 gms.) was normal except for small mononuclear infiltrates near some glomeruli and surrounding the blood vessels between the cortex and medulla. A few casts were present in the lower collecting tubules.

The remaining kidney after 58 days (wt. 36 gms.) was slightly edematous. The tubules were separated and contained moderate amounts of fluid. The groundwork of many glomerular tufts was indistinct. Considerable desquamation of swollen epithelium was observed in some of the tubules. Areas of beginning focal necrosis were noted in occasional proximal convoluted tubules.

¹Zenker's solution prepared with solution of formaldehyde instead of glacial acetic acid (Helly's fluid).

Dog 30 (wt. 7.8 kg.).--The control kidney (wt. 19.7 gms.) was normal. The remaining kidney after 179 days (wt. 23.5 gms.) was also normal except for a few small round cell infiltrates in the cortex.

Dog 50 (wt. 14 kg.).--Microscopic examination of the control kidney (wt. 36.5 gms.) revealed marked focal pyelonephritis. Many of the glomerular loops were fused together and contained an increased number of cells. There were numerous foci of interstitial cellular infiltration in the medulla and a considerable degree of scarring throughout the kidney. Some glomeruli were hyalinized; others were atrophic, and the corresponding tubules were shrunken. There was mild leukocytic infiltration below the epithelium of the renal pelvis. The major arteries were normal.

The remaining kidney after 180 days (wt. 35.2 gms.) presented a similar appearance, although the inflammation was not as severe. Large areas of leukocytic infiltration extended from the cortex to the upper part of the medulla. There were many atrophic glomeruli and tubules.

Dog 99 (wt. 16 kg.) (Fig. 1 A).--The control kidney (wt. 31 gms.) was normal. The remaining kidney after 365 days (wt. 32 gms.) was also normal except for one old cyst in the medulla with surrounding leukocytic infiltration.

It will be noted that in these animals the removal of one kidney was not followed by compensatory hypertrophy of the other.

Group Given Sodium Bicarbonate by Mouth

Minor changes appeared in the kidneys of the dogs given sodium bicarbonate by mouth only.

Dog 47 (wt. 8.9 kg.).--This animal was given 610 gms. of sodium bicarbonate in 30 days. The control kidney (wt. 24 gms.) presented evidence of chronic pyelonephritis. Tremendous sub-epithelial leukocytic infiltrates and many large areas of fibrosis extended through the cortex to the medulla. Many glomeruli were atrophic; the capsular spaces were distended and contained protein precipitate. The corresponding tubules were shrunken. The epithelium of the ascending limbs was vacuolated.

The "alkali kidney" (wt. 27.1 gms.) was similarly involved, although the inflammation was less marked. There were many small glomeruli. The fibrosis and scarring resembled those found in the control. In the upper part of the medulla, a number of the tubules were dilated and contained casts. In one area, the epithelium lining the tubules was necrotic. The pyelonephritis observed in the control kidney appeared to be less extensive after the ingestion of alkali.

Dog 42 (wt. 6.8 kg.).--This animal received 740 gms. of sodium bicarbonate in 42 days. The control kidney was normal (wt. 23 gms.). The "alkali kidney" (wt. 29 gms.) was moderately edematous. The glomeruli were normal. Protein precipitate was present in some of the tubules. The epithelium of the tubules in the inner cortex was mildly desquamated. A few masses of necrotic epithelium were noted in the upper part of the medulla. The only definite change, therefore, in the "alkali kidney" was the development of edema.

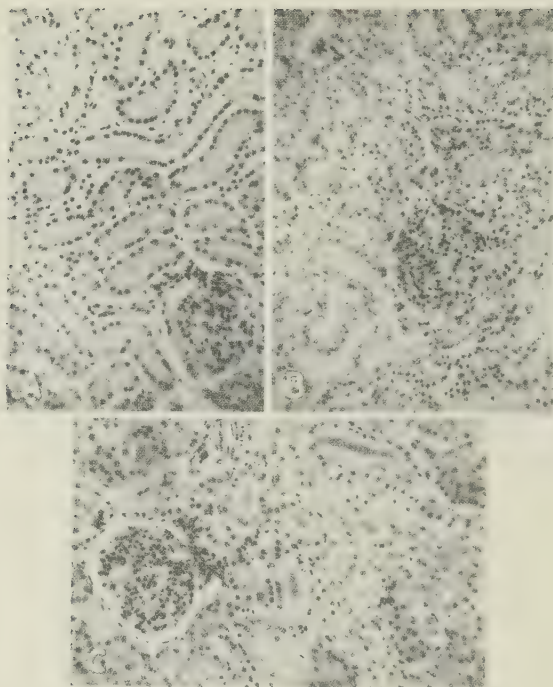


Fig. 1.--A (dog 99; no alkali), remaining kidney after 365 days. Granular material may be seen in the tubules. X250. B (dog 88), remaining kidney after 1,135 gms. of sodium bicarbonate had been given in 54 days. A hyperemic glomerulus and normal tubules are seen. C (dog 46), remaining kidney after 6,789 gms. of sodium bicarbonate had been given in 149 days. The glomerulus is normal. Note the dense granular masses in collecting tubules. X250.

Dog 88 (wt. 9 kg.).--This animal was given 1,135 gms. of sodium bicarbonate in 54 days (Fig. 1 B). The control kidney (wt. 25 gms.) showed evidence of active filtration in that the glomerular spaces and tubules contained moderate amounts of fluid. Irregular, blue-staining masses were present in some of the collecting tubules (probably necrotic epithelium). The glomeruli and tubules were normal.

The "alkali kidney" (wt. 26.2 gms.) was hyperemic. A few of the glomeruli were hyalinized, but the vast majority showed no change. Granular, dense blue-staining masses were observed in the lower collecting tubules, which were otherwise normal.

Dog 80 (wt. 7.5 kg.).--This animal received 1,795 gms. of sodium bicarbonate in 66 days. The control kidney (wt. 15.8 gms.) showed evidence of previous inflammation. Occasional scars ex-

tended from the cortex to the medulla. There was perivascular cellular infiltration in the upper part of the medulla. Focal cellular infiltrates were noted in the lower part of the cortex and in the medulla. The glomeruli and tubules were normal.

The "alkali kidney" (wt. 15 gms.) was less involved; there were only a few cellular infiltrates in the lower part of the cortex. The glomeruli and tubules were normal.

Dog 58 (wt. 6 kg.).--This animal was given 3,495 gms. of sodium bicarbonate in 114 days. The control kidney (wt. 16 gms.) was normal except for scattered areas of interstitial cellular infiltration in the lower part of the cortex and the upper part of the medulla.

The "alkali kidney" (wt. 20 gms.) was congested. There were several small cellular infiltrates in the upper part of the medulla. The glomeruli and tubules were normal.

Group Given Sodium Bicarbonate by Mouth and by Vein

The observations on the four dogs are of particular interest since, in addition to the daily oral administration of alkali, a weekly intravenous injection of sodium bicarbonate was given, producing moderately severe alkalosis.

Dog 94 (wt. 8.2 kg.).--This animal received 5,800 gms. of sodium bicarbonate orally and 250 gms. intravenously, the latter in eighteen divided weekly injections over a period of 125 days. The control kidney (wt. 32 gms.) was normal except for the presence of a few vacuolated cells in the epithelium lining the tubules in the lower part of the cortex.

The "alkali kidney" (wt. 34.5 gms.) was moderately edematous, and protein precipitate was present in all the convoluted tubules. The glomeruli and tubules were normal.

Dog 66 (wt. 9.6 kg.).--This animal received 5,245 gms. of sodium bicarbonate orally and 67 gms. intravenously, the latter in four divided weekly injections over a period of 149 days. The control kidney showed no changes except for the presence of large foam-shaped cells in the tubules. The remainder of the kidney was normal.

The "alkali kidney" (wt. 16 gms.) was edematous. A protein precipitate was present in some of the convoluted tubules. In one area, many hyaline casts were seen in the tubules; the epithelium of the tubules, however, was normal. The glomeruli and major arteries were also normal.

Dog 46 (wt. 5.2 kg.).--The animal was given 6,530 gms. of sodium bicarbonate orally and 259 gms. intravenously, the latter in twenty divided weekly injections over a period of 149 days (Fig. 1 C). The control kidney (wt. 17.5 gms.) was essentially normal. Some of the glomeruli and many of the tubules contained a fine precipitate.

In the "alkali kidney" (wt. 26.6 gms.) the glomeruli and major arteries were normal. Numerous, granular, blue-staining masses were seen in the distal and collecting tubules. The tubular epithelium contained many dark nuclei, but the cell outlines were distinct. An attempt to stain the sections for calcium was unsuccessful because of the method of fixation. It was impossible, therefore, to decide whether these granular masses repre-

sented either necrotic epithelium or areas of calcification.

Dog 33 (wt. 10.7 kg.).--This animal received 11,220 gms. of sodium bicarbonate orally and 381 gms. intravenously, the latter in 21 divided weekly injections over a period of 261 days (Fig. 2). The control kidney (wt. 29.5 kg.) was normal except for the presence of deeply staining granular masses in the tubules in the lower part of the medulla. A protein precipitate was present in a few of the glomerular and tubular spaces.

The "alkali kidney" (wt. 37.3 kg.) was markedly hyperemic. There was focal scarring. An occasional glomerulus was hydro-nephrotic. The tubular capillaries were dilated, and many tubules contained a protein precipitate. There was moderate localized desquamation of the tubular epithelium. Numerous, granular, blue-staining masses were found in the collecting tubules.

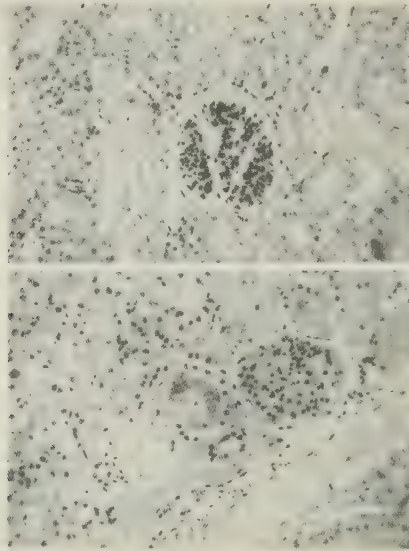


Fig. 2.--(Dog 33). A, control. The glomerulus and tubules are normal. B, remaining kidney after 11,601 gms. of sodium bicarbonate had been given in 261 days. Note hyperemia of the glomerulus and dense granular masses in collecting tubules. The epithelium of the latter is partially desquamated.

Of interest in these dogs was the absence of inflammatory changes in the gastric mucosa. This finding is in contrast to the clinical belief that prolonged ingestion of alkalis results in gastritis.

COMMENT

Previous investigations have suggested that, while albumin, casts, or red blood cells may appear in the urine, no significant anatomic changes occur in the kidneys after the administration of sodium bicarbonate. Many of these experiments, however, especially those of Fischer, Kellert, and Suzuki, are of little value in assessing the possible effects of the prolonged use of alkalis, since they consisted in the administration of a single large dose of sodium bicarbonate. The only long-continued administration of alkalis, except for the present study, was that carried out by Addis, MacKay, and MacKay in rats, and, although these investigators observed hematuria and hydronephrosis in some of their animals, the microscopic changes did not differ markedly from those of the control group. The present investigation differs from previous studies on three important points: For the first time dogs were employed as the test animals. Since the dog's kidney reacts functionally in a manner somewhat similar to that of the human kidney, the present experiments are perhaps more analogous to the problem in man. Secondly, control histologic examinations of the kidneys of the test animals were made possible by preliminary unilateral nephrectomy. The value of these control studies is demonstrated by the fact that in two dogs not given an alkali and in four which later received sodium bicarbonate the control kidneys showed evidence of previous injury--lesions which obviously could not be related to the effect of the alkali. The removal of one kidney also increased the excretory activity of the remaining kidney, and thereby provided a more rigid test of the effect of the alkali. Thirdly, large amounts of sodium bicarbonate were given orally and in four dogs also intravenously to insure the presence of continued alkalosis. In view of these stringent experimental conditions, it is noteworthy that no marked anatomic renal changes were observed after the administration of sodium bicarbonate. Edema and hyperemia of the kidney were noted in six of the alkali-treated dogs. The edema was apparently caused by the fluids injected intravenously and also by the circulatory congestion associated with the convulsions appearing during the acute alkalosis. Moderate amounts of a protein precipitate were noted in the glomerular spaces and tubules of the kidneys of three dogs, suggesting that albumin may

have been present in the urine during life. However, since both hyperemia and protein precipitate may appear very rapidly as acute antemortem changes, these observations cannot be considered indicative of chronic renal injury. Granular, dense, blue-staining masses were seen in the lumens of the collecting tubules in three dogs. A similar, although less marked, alteration was observed in the control kidneys of two of these animals. In the absence of specific calcium stains the differentiation of these masses either as necrotic epithelium or as foci of calcification was not possible. It is possible, however, that the sodium bicarbonate was at least partially responsible for the appearance of these granular masses, since they were most numerous in the two dogs receiving the largest quantities of alkali (46 and 33). In dog 66 a few tubules contained many hyaline casts. In dog 33 the epithelium lining one section of tubules was moderately desquamated. This finding was the only sign suggestive of renal injury following the administration of sodium bicarbonate obtained in this study, but it was present to fully as great an extent in a control animal.

It is a well-known fact that the functional behavior of the kidney often cannot be correlated with its anatomic appearance. It is possible, therefore, that clinical tests may indicate the presence of renal injury undetectable by present histologic methods. On the other hand, the results of the present study, demonstrating the absence of marked renal injury after the administration of sodium bicarbonate, are in accord with the observations noted in previous sections of this thesis indicating that the urea clearance is not lowered permanently either by alkalosis or by the prolonged ingestion of alkali.

CONCLUSION

The administration of large quantities of sodium bicarbonate by the oral and intravenous routes for periods as long as nine months does not produce marked or chronic anatomic change in the kidney of the dog.

B. THE EFFECT OF PROLONGED ALKALI THERAPY AND
OF ALKALOSIS ON THE STRUCTURE OF THE
HUMAN KIDNEY: AUTOPSY OBSERVATIONS

METHOD OF STUDY

The present investigation comprises a study of the autopsy findings in 14 patients who had received during life large quantities of alkali and in whom adequate studies of the acid-base balance were available. The series is composed of four patients (Group I) who had taken large amounts of alkali but in whom alkalosis had never occurred; six patients (Group II) who had experienced one or more episodes of alkalosis during alkali therapy but who did not die in alkalosis; five of this group died of other complications several weeks after alkalosis, while the sixth patient died ten months after a severe alkalosis; and four patients (Group III) who had taken large quantities of alkali and in whom alkalosis had been present at the time of death.

RESULTS

Group I. Prolonged Alkali Therapy--No Alkalosis

Case 1.--C. J. P. (Unit no. 143448), a 52-year-old male, had been treated for ulcer symptoms for seven years during which time he had received large amounts of alkali. He entered the hospital because of a severe hemorrhage which proved fatal on the twenty-ninth day despite six blood transfusions and the subcutaneous administration of 5% glucose and normal saline solutions. Five hundred and eighty-five grams of sodium bicarbonate and calcium carbonate were administered during the first 15 days; the patient received no alkali during the last 14 days. The acid-base balance was normal. There was no elevation of the blood urea or nonprotein nitrogen and the urea clearance was 69% of average normal. The urine contained hyaline and granular casts.

Necropsy revealed a benign peptic ulcer of the lesser curvature of the stomach with recent thrombosis of the artery in the floor of the ulcer; acute distention of the right side of the heart with acute generalized passive hyperemia most evident in the kidneys; pulmonary edema; right hydrothorax; ascites; moderate

sclerosis of the aorta and coronary arteries.

The kidneys were purplish in color and firm; the right weighed 185 gms. and the left 160 gms. The capsule stripped easily leaving a smooth surface. The parenchyma was very cyanotic. Microscopic examination revealed only mild arterio-sclerotic changes.

Case 2.--G. L. (Unit no. 162012), a 56-year-old male, had suffered from high blood pressure for at least four years. One year, five months, and one month previously he had experienced three hemorrhages arising from a gastric ulcer. Alkalis had been taken intermittently during this time. He entered the hospital with another massive hemorrhage. Therapy included two blood transfusions and 1521 gms. of sodium bicarbonate and calcium carbonate given over a period of 39 days. The acid-base balance was normal. The blood urea nitrogen was 9.6 mg.% and the urea clearance 89% of average normal; nine urine examinations were negative. The patient returned two months later because of a recurrent gastric ulcer, hypertensive vascular disease, and hypertensive retinitis. Alkalis had been taken occasionally. The blood pressure now was 188/120. Three hundred and ninety-three grams of sodium bicarbonate and calcium carbonate were administered in nine days. The acid-base balance remained normal; the blood urea nitrogen measured 14 mg.%. Six urine specimens were negative. One year after the initial entry the patient returned for a third time. He received, over a period of 59 days, 2301 gms. of sodium bicarbonate and calcium carbonate. The blood urea nitrogen was 12.3 mg.% and the urea clearance 94% of average normal. A carcinoma of the stomach was discovered at this time from which the patient died several months later.

Necropsy revealed a diffusely infiltrating carcinoma of the stomach with pyloric obstruction; a healed benign gastric ulcer in the prepyloric region and a chronic benign ulcer high on the lesser curvature with fixation to the tail of the pancreas; bronchopneumonia of the right upper pulmonary lobe and an early abscess in the right lower lobe; bilateral hydrothorax; arterio-sclerosis of the aorta.

The kidneys each weighed 140 gms.; they were flabby in consistency. The capsule stripped readily leaving a uniformly granular, pale purple-gray colored surface. A few small cysts were present on the surface. The cortex measured 3-4 mm.; the cortico-medullary demarcation and the cortical markings were obscured. Several small cysts were located in the medulla. The renal pelvis and ureters were normal. Microscopic examination re-

vealed a few areas of scarring with foci of round cells. Some of the glomeruli showed varying stages of hyalinization; the associated tubules were atrophied. The tubules, especially in the cortex, showed moderate fatty changes and contained protein debris and hyaline casts. There was some increase in interstitial fibrous tissue. The arteries and arterioles showed varying degrees of sclerosis.

Case 3.--C. T. (Unit no. 164916), a 62-year-old man, had experienced ulcer distress for ten years. Alkalis had been taken regularly for about one year and then intermittently during the subsequent nine years. He entered the hospital because of a severe hemorrhage and for the initial five days was treated with alkalis, receiving 320 gms. of calcium carbonate. Six blood transfusions were given. A subtotal gastrectomy was performed because of persistent massive hemorrhage. The patient continued to bleed, however, and he died shortly after the operation. There was no alkalosis.

Necropsy revealed a large, chronic, benign ulcer on the posterior wall near the cardiac portion of the stomach, close to the greater curvature; perforation of an aneurysm of a short gastric artery located in the floor of the ulcer; marked parenchymatous changes in the myocardium with moderate dilatation; focal necrosis of the liver; marked bilateral hypostatic pulmonary edema with aspirated blood and probably beginning bronchopneumonia.

Each kidney weighed 130 gms.; the surrounding fat and capsule stripped easily. The capsular surfaces were smooth except for a few tiny retention cysts. The vascular markings were fairly well preserved. The renal pelves were normal. The chief microscopic findings were scattered hyalinized glomeruli and slight fibrous thickening of the walls of the larger arteries. Occasional cortical tubules showed fatty degeneration.

Case 4.--A. M. (Unit no. 185319), a 57-year-old male, had experienced gastrointestinal distress for 15 years. One year prior to entry he had been treated with moderate amounts of alkali following the appearance of tarry stools. Sodium bicarbonate had been taken occasionally for three weeks prior to entry. The patient received a total of 1212 gms. of sodium bicarbonate and calcium carbonate over a period of 23 days. He died on the twenty-fourth day as a result of coronary thrombosis. The acid-base balance was normal. The blood urea nitrogen was 14.8 mg.% and the urea clearance 78% of average normal. One of ten urine specimens contained albumin.

Necropsy revealed multiple healed infarcts of the myocardium; marked coronary sclerosis with recent rupture of a

plaque; peptic ulcer of the first part of the duodenum; cardiac hypertrophy and dilatation; congestion of the liver and spleen; nodose goiter with solitary cyst.

The kidneys each weighed 240 gms. and were very firm. The capsule stripped easily leaving a smooth, pale red surface with a few up to 5 mm. cysts, and small, irregular, stellate, depressed scars. The cut surface appeared cyanotic. The cortex was 7 mm. wide; the cortico-medullary demarcation was distinct, although the other markings were not clear. Microscopic examination revealed scattered hyalinized glomeruli and focal round cell infiltration. Protein debris was present in the lumina of the tubules. The epithelium of the tubules contained small amounts of fat. There was moderate sclerosis of the blood vessels and marked dilatation and congestion of the capillaries.

Comment.--No significant renal changes were noted in these four patients despite the prolonged use of considerable quantities of alkali. The hyalinized glomeruli and atrophied tubules observed in Cases 2 and 4 are usual autopsy findings in patients of this age. The focal fatty degeneration of the tubular epithelium and the presence of protein precipitate and hyaline casts observed in two of the patients are acute changes attributable to the passive congestion and anemia.

Group II. Prolonged Alkali Therapy with Alkalosis Death Caused by Other Complications

Case 1.--J. P. (Unit no. 77800), a 60-year-old man, had experienced ulcer distress for four years. He occasionally took sodium bicarbonate and frequently induced vomiting to obtain relief from pain. He entered the hospital because of a severe hemorrhage and died 16 days later despite eight blood transfusions. Six hundred and ninety-five grams of sodium bicarbonate, calcium carbonate, and tricalate were administered during this period. Studies of the acid-base balance revealed a moderate alkalosis on the third day (CO_2 36.6 mM/L and pH 7.53); this became severe on the seventh day when the serum CO_2 measured 46.3 mM/L and the pH 7.63. The alkalosis subsided rapidly after cessation of alkali therapy and the administration of ammonium and sodium chloride by mouth. Alkali therapy (tricalate) was resumed on the tenth day but the acid-base balance remained normal. The blood urea nitrogen, which had risen to 46.8 mg.% on the eighth day, decreased to 19.4 mg.% one week later. The urea clearance values ranged from 40 to 79% of average normal. The blood creatinine fluctuated between 1.29 and 1.88 mg. Seven urine examinations were negative.

Necropsy revealed a massive hemorrhage into the stomach and duodenum from a branch of the superior pancreatico-duodenal artery located in the floor of a large duodenal ulcer; the lungs and retroperitoneal tissues were markedly edematous and both pleural cavities contained fluid.

The kidneys were embedded in considerable adipose tissue; together they weighed 320 gms. The capsule stripped easily leaving a smooth surface. The cortex was extremely pale and measured 5 to 6 mm.; the medulla measured 15 mm. The cortical markings were fairly distinct. The renal pelvises were normal. Microscopic examination revealed most of the glomeruli to be normal; fat stains demonstrated a few foci of slight fatty degeneration in the tubules. There was moderate intimal thickening of the larger arteries and extreme thickening of some arterioles.

Case 2.--C. F. D. (Unit no. 96955), a 54-year-old male, had experienced ulcer distress for 18 years for which sodium bicarbonate had been taken frequently. He was hospitalized for 21 days and during the first nine days received 137 gms. of sodium bicarbonate and calcium carbonate. Symptoms of alkalosis appeared on the ninth day. The serum CO_2 at this time was 46.5 mM/L and the pH 7.58. The blood urea nitrogen increased from 9.2 mg.% to 18.1 mg.% and the urea clearance, previously 63% of average normal, decreased to 37%. Alkalis were stopped for six days and sodium and ammonium chloride were given by mouth. The acid-base balance returned to normal in six days; the blood urea nitrogen decreased to 10.9 mg.% and the urea clearance increased to 65%. Tricalsate then was substituted for the previous alkali and the patient's subsequent clinical course was uneventful. He died ten months later, however, following an operation for carcinoma of the gall bladder.

Necropsy revealed a carcinoma of the gall bladder with metastases to the liver and perihepatic lymph nodes; hemorrhage into the duodenum from a duodenal ulcer; bilateral pulmonary edema.

The kidneys were of about equal size and together weighed 300 gms. The capsule stripped easily leaving a smooth surface. The cortex was slightly brown in color; the cortical markings were preserved. Microscopically the glomeruli were normal. There was no significant change in the tubular epithelium. The only microscopic finding was a slight diffuse subcapsular scarring with round cell infiltration.

Case 3.--L. D. (Unit no. 194530), a 38-year-old male, had had a stenosing duodenal ulcer for 15 years complicated by a massive hemorrhage eight years previously. He had vomited frequently since that time and often had required sodium bicarbonate

for the relief of ulcer distress. His blood pressure was found to be 190/130. During the first 17 days, 1292 gms. of alkali, mainly sodium bicarbonate, were given. A partial gastrectomy was performed on the eighteenth day because of obstruction. The patient vomited persistently and he died several days later despite the parenteral administration of large quantities of normal saline and 5% glucose solutions. The serum CO_2 and pH were elevated slightly on the fifth hospital day; the blood urea nitrogen was 25.5 mg.% and the urea clearance 39% of average normal. Two of six urine specimens contained hyaline and granular casts, albumin, and occasional red and white blood cells.

Necropsy revealed a chronic duodenal ulcer with adherence to the pancreas; dilatation of the duodenum; torsion and gangrene of the proximal anastomosed jejunal loop with dilatation, hemorrhage, and venous thrombosis; hemoperitoneum; cardiac hypertrophy.

The kidneys each weighed 160 gms.; they were markedly pale, gray-white in color, and firm. The capsule stripped easily leaving a smooth surface. The cortex measured 5-6 mm.; the cortical markings were distinct. On microscopic examination, many of the glomeruli showed varying degrees of hyalinization and some were partially or completely adherent to the capsules. There was marked thickening of Bowman's capsules. The epithelium of some of the collecting tubules showed mild degenerative and regenerative¹ changes and the lumina of these tubules contained blue staining masses (with the hemotoxylin and eosin stain), suggesting calcium. Protein precipitate was noted occasionally. There was a definite increase in the interstitial fibrous tissue; scattered foci of round cells were present. Both the large and small renal arteries showed intimal proliferation.

Case 4.--C. A. M. (Unit no. 128123), a 34-year-old male, had experienced ulcer symptoms for five years during which time he had taken moderate amounts of sodium bicarbonate. Hypertension had been present for at least six years. He entered the hospital with a severe hemorrhage, and received over a period of 49 days, 2700 gms. of alkali consisting of sodium bicarbonate, calcium carbonate, and tricalsate. Studies of the acid-base balance revealed a mild alkalosis. Renal function was impaired, the urea clearance values ranging from 26 to 47% of average normal. The blood urea nitrogen rose to 43.8 mg.%, but gradually decreased by the forty-fourth day to 12.3 mg.%. After recovery from the hemorrhage the patient was continued on a modified ulcer

¹Regenerative changes accompanying degeneration of the epithelium of the renal tubules are frequently observed. Experimentally, they have been noted to occur within a period of seven days (11).

regime with tricaltsate for five months. At this time he experienced a second severe hemorrhage from which he died on the thirty-second day. Twenty-four hours before death the patient experienced a transfusion reaction characterized by a chill and a temperature rise to 106 degrees. Treatment had included small amounts of sodium bicarbonate, the subcutaneous administration of normal saline and 5% glucose, and nine blood transfusions. There was no evidence of alkalosis at this time. The blood urea nitrogen, however, ranged from 40.2 to 113.2 mg.% and the urea clearance from 9 to 24% of average normal. The blood creatinine varied from 2 to 3 mg.%. Five of nine urine specimens contained a trace of albumin; the maximum specific gravity was 1018.

Necropsy revealed an acute duodenal ulcer with recent massive hemorrhage; a chronic healed duodenal ulcer; marked cardiac hypertrophy, especially of the left ventricle; marked pulmonary edema with early bronchopneumonia; parenchymatous degeneration of the liver and myocardium; moderate sclerosis of the aorta, coronary, and medium-sized arteries.

The right kidney weighed 90 gms. and the left 110 gms.; they were flabby and pale. The capsule stripped easily leaving a finely granular surface with numerous punctate hemorrhages. The cortices were somewhat decreased in width and the cortical markings were indistinct. The renal pelves were normal. Microscopic examination revealed a marked increase in fibrous tissue with diffuse and focal round cell infiltration. Many of the glomeruli showed varying degrees of hyalinization. Many of Bowman's capsules were thickened. These changes were associated, especially in the cortex, with groups of markedly dilated tubules, the epithelium of which was flat and cuboidal. Hyaline casts were noted frequently. No calcium precipitate was visible. Fat stains disclosed a focal fatty degeneration of the tubular epithelium. The arteries and arterioles were markedly sclerosed and the walls of the arterioles showed a severe fatty degeneration.

Case 5.--W. R. (Unit no. 105146), a 57-year-old male, entered the hospital because of a massive hemorrhage from a gastric ulcer. No alkalis had been taken previously. He remained in the hospital for 66 days during which time he received a total of 2700 gms. of sodium bicarbonate and calcium carbonate. Nine urine examinations were negative. The serum CO_2 measured 33.6 mM/L and the pH 7.58 on the seventh hospital day. He returned three and one-half years later with a recurrent ulcer; alkalis had been taken during the interim. The patient received 2574 gms. of sodium bicarbonate and calcium carbonate over a period of 66 days. Studies of the acid-base balance on the third, eleventh, and

twenty-eighth days revealed a mild to moderately severe alkalosis, the serum CO_2 ranging from 32.4 to 37.8 mM/L, the pH from 7.51 to 7.63, and the chloride from 90.6 to 98.2 mM/L. The blood urea nitrogen varied from 15.8 to 20.8 mg.% and the urea clearance from 41 to 109% of average normal. Eleven urine examinations were negative. Six months later (four years after the initial entry) the patient again was hospitalized because of a recurrent hemorrhage; alkalis had been taken occasionally during this interval. He remained in the hospital for twenty-one days, receiving a total of 6933 gms. of alkali (mainly calcium carbonate) almost entirely during the first 173 days. Aspiration of the gastric contents yielded from 300 to 400 cc. nightly. Many determinations of the acid-base balance and renal function (urea clearance) were made (see Table 1). Twenty-seven urine examinations were negative; the maximum specific gravity was 1030. During the last 80 days in the hospital the patient's clinical course was complicated by the development of an auricular flutter. He also experienced severe bouts of coughing. Cyanosis, which had been present to a mild degree, increased. Treatment included the parenteral administration of 5% glucose and normal saline solutions, and blood transfusions. The patient, however, did not improve and he was found dead in bed on the 211th hospital day.

Necropsy revealed a marked atrophic pulmonary emphysema; senile pulmonary bullous emphysema with marked hypertrophy of the right myocardium (cor pulmonale); acute pulmonary edema; acute distention of the right ventricle with acute generalized passive congestion; "nutmeg" liver; chronic induration of the spleen; bilateral hydrothorax; massive benign peptic ulcer of the lesser curvature in the prepyloric area of the stomach; chronic atrophic gastritis; old perforative peptic ulcer with adhesions to the liver; moderate sclerosis of the pulmonary artery and of the aorta.

The right kidney weighed 180 gms., the left 155 gms. The cortical markings were somewhat obscured. The capsule stripped readily from a smooth, pale surface. There appeared to be an increased amount of yellowish white material in the cortex and pyramids. The renal pelves and ureters were normal. On microscopic examination, most of the glomeruli were normal. A few were hyalinized and the corresponding tubules atrophied. Considerable protein precipitate was present in Bowman's capsules. The epithelium of the convoluted tubules was markedly swollen so that the lumen was almost obliterated in occasional areas. Some of the nuclei were hyperchromatic while others had disappeared.

Occasional hyaline casts were visible in the collecting tubules. A few of the collecting tubules contained blue-staining material suggesting calcium; small foci of round cells occasionally surrounded these tubules. There was a marked fatty degeneration particularly of the collecting tubules, although some of the convoluted tubules also were affected.

Case 6.--S. S. M. (Unit no. 211271), a 52-year-old male had experienced ulcer distress for three years during which time he had had four hemorrhages. Large amounts of alkali were taken by the patient. Treatment included 400 gms. of calcium carbonate and magnesium oxide given during the first twenty-two days, and aspiration of the stomach daily for the same length of time, the aspirates averaging 300 cc. in amount. On the twenty-third hospital day a cholecystectomy and posterior gastroenterostomy were performed for cholelithiasis and an obstructing duodenal ulcer. No alkali was given postoperatively. The patient's course was complicated by a wound infection which was treated with sulfanilamide. The sulfanilamide was discontinued after four days, however, because of a toxic reaction. Large quantities of normal and 5% saline, Ringer's, and 5% glucose solutions were given parenterally. Wangensteen suction of the stomach was carried out for fourteen days postoperatively, the quantities removed varying from 500 to 3000 cc. in amount daily. A number of urine specimens contained albumin. Determinations of the acid-base balance and renal function (urea clearance) were made frequently (see Table 2). The patient gradually became worse and he died on the fifty-sixth postoperative day of a bronchopneumonia.

Necropsy revealed a generalized, latent, osteitis fibrosa cystica; hyperplasia of the parathyroid glands (3); pyloric stenosis; bronchopneumonia of the right lower pulmonary lobe; generalized arteriosclerosis.

The kidneys were small, and pale in color; together they weighed 165 gms. The capsule stripped easily from a smooth surface. The cortical markings were obscured. The pelvic fat was increased and each renal pelvis was dilated and thick-walled. The calyces were large and clubbed on the ends. The ureters were normal. Microscopic study revealed distinctly abnormal kidneys. The tips of the pyramids were not recognizable. In the cortex many wedge-shaped areas of scarring and chronic inflammation alternated with more normal areas. The ratio of scarred to normal tissue was estimated to be 1:2. Remnants of hyalinized glomeruli and some partially hyalinized and shrunken tubules were visible in the scarred areas. The inflammatory cells of the scars consisted mostly of small mononuclears and lymphocytes. Most of the glomeruli in the more normal areas were well preserved. The tubular epithelium in the well-preserved regions varied from flat

cuboidal to tall cells; the nuclei varied greatly in size. Many of the tall cells contained pale, granular, or vacuolated cytoplasm and some contained colloid droplets. Casts were infrequent and there was little protein debris. Numerous cast-filled and cast-obstructed collecting tubules were seen. Most of the casts were composed of deep blue or blue-purple staining, granular masses forming dense aggregates, suggesting calcium. Similar masses were present in the interstitial tissue with no recognizable tubular membrane surrounding them. These were associated with an increase in fibrous tissue but little inflammatory reaction. The larger arteries were moderately hyalinized but not greatly narrowed. The small arteries, especially in the scarred regions, were thickened.

Comment.--No significant renal changes were noted in Cases 1 and 2 despite the previous existence of a severe alkalosis. The presence of scattered hyalinized glomeruli and focal fatty degeneration in the tubular epithelium are usual necropsy findings in patients of this age.

The alkalosis in Cases 3 and 4 had been mild. The hypertension which had been present in both patients undoubtedly accounted for all the changes described. An additional observation in Case 3 was the presence in a few collecting tubules of blue-staining material, suggestive of calcium; this finding is discussed later.

Case 5 constitutes one of the most interesting of the entire series. This individual had consumed enormous quantities of alkali, receiving during three hospital periods alone, 12,207 gms. of sodium bicarbonate and calcium carbonate. Large amounts of gastric contents had been aspirated daily and the patient had experienced one episode each of mild, moderate, and severe alkalosis. There was little anatomic evidence of chronic renal injury despite these factors. Most of the glomeruli were normal. The swelling of the tubular epithelium with focal necrosis and fatty degeneration and the presence of protein precipitate and hyaline casts all are attributable to the marked passive congestion. Blue-staining material was visible in occasional collecting tubules in this case also.

Case 6 is likewise of considerable interest. The aspiration of large quantities of gastric contents undoubtedly had contributed to the development of the severe alkalosis. It should be emphasized that this patient exhibited clinical evidence of renal impairment at the onset of therapy. Many of the renal changes were arteriosclerotic in origin. Most of the glomeruli and approximately two-thirds of the entire kidney substance ap-

peared normal, however. The most striking observation was the presence of blue-staining material in numerous collecting tubules, some of which were obstructed and surrounded by an increased amount of interstitial fibrous tissue. Similar blue-staining material was visible also in the interstitial tissue itself suggesting possibly a primary type of calcification in contrast to calcium precipitation. The parathyroid hyperplasia presumably was secondary to the renal insufficiency. The role of sulfanilamide toxicity in the pathogenesis of the renal changes cannot be evaluated but, on the other hand, cannot be completely excluded.

Group III. Prolonged Ingestion of Massive Quantities of Alkali--Died in Alkalosis

Case 1.--R. H. (Unit no. 159494), a 59-year-old male, had for three years frequently required sodium bicarbonate for the relief of ulcer symptoms. He was hospitalized for 14 days during which time he received a total of 609 gms. of sodium bicarbonate, calcium carbonate, and tricalcate. A moderately severe chemical alkalosis was noted on the fifth and ninth days. One year and seven months later the patient's symptoms recurred, and he was instructed to take alkalis at hourly intervals and to aspirate his stomach each night. This program was continued for two months; the gastric aspirations varied in amount from 3 to 6 ounces. Several days before hospitalization he began to vomit large amounts of gastric content and, just prior to entry, the patient became disoriented and semicomatose. He was markedly dehydrated and emaciated; the blood pressure which formerly had been 140/85, now was 80/52. Massive quantities of normal and 5% saline, and 5% glucose solution were administered subcutaneously and intravenously. Two blood transfusions also were given. The patient failed to respond to this therapy; he became markedly cyanotic and died on the fifth hospital day. The serum CO_2 on the third day measured 42.6 mM/L; this diminished to 33 mM/L 24 hours later. The blood chloride increased from 494 to 653 mg.%, while the non protein nitrogen varied between 140 and 146 mg.%.

Necropsy revealed a chronic duodenal ulcer near the pylorus, marked duodenal stenosis exaggerated by kinking due to traction of the stomach on the hepato-duodenal ligament; gastric hypertrophy and dilatation; slight cardiac dilatation; marked, bilateral, hypostatic pulmonary hyperemia and edema; acute aspira-

tion bronchopneumonia with beginning suppuration in the right lower lobe; fatty degeneration and hemosiderosis of the liver; extreme edema of the entire gastrointestinal tract; ascites; minimal senile arteriosclerosis.

The kidneys were dark purple-gray in color and firm; the perirenal fat was slightly adherent; the right weighed 100 gms. and the left 120 gms. The capsule stripped easily leaving a very cyanotic surface with prominent stellate veins. The cortex was dark reddish-purple in color; the cortical rays were indistinct; the cortex measured 6 mm. The cortico-medullary area was very dark; the tips of the pyramids were quite pale and fibrous. Microscopic examination revealed a few foci of scarring under the capsule with occasional round cell infiltration. There was a marked increase in interstitial fibrous tissue in the medullary pyramids. Occasional scattered glomeruli were hyalinized but the majority were practically normal. Bowman's spaces were well-filled and nowhere were greatly dilated. Many of the tubules in the cortex had wide lumens and flat epithelium, and usually contained protein debris. A few tubules in the scarred areas of the kidney were atrophic. Throughout the cortex, single or several tubules contained epithelium with large, pleomorphic nuclei. Occasional tubules contained pale to dark blue-staining granular masses. A few of these masses appeared to be obstructing tubules, the epithelium of which was flat or focally missing. The obstructed tubules were located usually not far from the cortico-medullary junction; none was recognized in Henle's loops. There was no marked sclerosis of the large or small arteries. Sharlach red stains demonstrated a slight fatty degeneration of the tubular epithelium.

Case 2.--A. R. (Unit no. 61840), a 49-year-old male, had experienced ulcer symptoms for seven years. Large amounts of alkali had been taken during this time. His right kidney had been removed six years previously because of a tuberculous infection. Just prior to hospitalization the patient had taken huge amounts of sodium bicarbonate and had vomited frequently. Forty-two grams of calcium carbonate were given during the first six days. The patient continued to vomit and on the seventh day the serum CO_2 measured 57.9 mM/L and the pH 7.69. He became slightly disoriented and was given 1000 cc. normal saline intravenously. On the eighth day the serum CO_2 was 49.2 mM/L and the pH 7.66; the blood urea nitrogen was 78 mg.%. Coma developed at this time and the patient was given 400 cc. of normal saline intravenously and 1500 cc. subcutaneously. Muscular fibrillations appeared and these were followed by a series of four convulsions. The blood pressure, which had been 160/85 on entry, rose to 300/125 and then gradually fell, first to 180/110 and then to 95/50. Auricular fibrillation associated with severe cyanosis was noted at this time. The cardiac irregularity disappeared after the administra-

tion of digitalis. On the ninth day the serum CO_2 measured 43 mM/L, the pH 7.53, and the blood urea nitrogen 90 mg.%. The blood pressure fluctuated from 125 to 135 systolic and 80 to 85 diastolic. On the tenth day the serum CO_2 was 31.4 mM/L, the pH 7.50, the creatinine 3.7 mg.%, and the blood urea nitrogen 98 mg.%. Death occurred on the tenth day as a result of cardiac failure. Several urine specimens contained occasional red and white blood cells.

Necropsy revealed two chronic peptic ulcers and one healing, superficial ulcer on the lesser curvature of the body of the stomach; cardiac dilatation, especially of the right chambers of the heart, with slight hypertrophy of the left ventricle; hypostatic hyperemia and edema of the lungs with acute bilateral bronchopneumonia; passive congestion of the liver with fatty changes; moderate generalized arteriosclerosis with sclerosis of the coronary arteries; focal myocarditis; encapsulated caseous and caseo-calcareous tuberculosis of the right epididymus; healed calcified tubercles in upper lobes of left lung, in left hilum lymph nodes, and peritracheal lymph nodes.

The remaining left kidney weighed 225 gms. The capsule stripped easily leaving a surface mottled with cyanotic and very pale areas; the cut surface bulged. The cortex measured 8 mm. and was somewhat mottled with pale areas in which the vascular markings were indistinct and darker areas where they were well preserved. The medulla was thinner than normal and the tips of the medullary pyramids were fibrous. Microscopically, the glomeruli were within normal limits. The tubules were slightly dilated and contained much protein precipitate, occasional granular and hyaline casts, and leukocytes. A few collecting tubules contained a crystalline material staining faintly blue with hematoxylin and eosin, suggesting calcium. The epithelium of these tubules showed mild degenerative and regenerative changes. Surrounding these cortical tubules were scattered foci of round cell infiltration. The arterioles and larger-sized arteries showed some thickening.

Case 3.--J. P. B. (Unit no. 17094), a 62-year-old male, had taken large amounts of sodium bicarbonate for many years for the relief of ulcer distress, averaging one pound of alkali per week during the past two years. Sixteen months ago he had been hospitalized elsewhere for five months because of severe epigastric pain and vomiting. The symptoms persisted and the patient entered Billings hospital. His blood pressure was found to be 222/116. During the first six days he received 150 gms. of sodium bicarbonate and calcium carbonate. On the seventh day, he became drowsy and irrational and was given 1000 cc. of normal

saline intravenously. The patient grew progressively worse, and he lapsed into a coma on the ninth day. Solutions of 5 and 10% glucose in normal saline were administered parenterally without avail and the patient died in cardiac failure. Gastric aspirations during the first six days yielded from 700 to 1000 cc. of gastric contents daily. Determinations of the acid-base balance revealed the presence of a severe alkalosis which persisted until the ninth day (see Table 3). Renal function was not determined; one urine specimen contained albumin.

Necropsy revealed a chronic, benign ulcer in the prepyloric region of the stomach; acute pulmonary edema; acute distention of the right side of the heart; acute passive hyperemia of the liver and kidneys; moderate sclerosis of the abdominal aorta.

The kidneys were moderately enlarged, together weighing 350 gms., and were of firm consistency. The capsule stripped easily leaving a smooth surface. The cortical markings were somewhat indistinct; the pyramids were cyanotic. The renal pelvises and ureters were normal. Microscopic examination revealed many hyalinized glomeruli. Focal hemorrhage and thrombosis of the glomerular tufts were noted occasionally; these changes were not far advanced. There was considerable degeneration of the tubular epithelium associated with fatty degeneration. Rare tubules were lined by hyperplastic epithelium; a few eosinophilic and hyaline casts were seen. There was moderate scarring of the interstitial tissue in the cortex especially just below the capsule. No calcium precipitation was observed. Some of the arterioles were markedly hyalinized while others appeared relatively normal. The large arteries showed only moderate sclerosis.

Case 4.--B. G. (Unit no. 119566), a 37-year-old woman, entered the hospital (1/18/35-2/2/35) with a history of ulcer distress for five years. Alkalis had been taken occasionally during this time. The blood pressure was elevated, ranging from 154 to 170 systolic and from 88 to 110 diastolic. Seven hundred and forty-three grams of calcium carbonate and 826 gms. of sodium bicarbonate were given in 25 days. Nine urine examinations were negative; the maximum specific gravity was 1021. The blood urea nitrogen measured 11.3 mg.% and the urea clearance 65% of average normal. Ulcer therapy was continued faithfully for the next year and the patient remained fairly well except for frequent episodes of vomiting. She was readmitted (2/11/36-4/10/36) because of a massive hemorrhage. Treatment included the use of parenteral fluids and continuous aspiration of the stomach each night. Six hundred and seventy-four grams of calcium carbonate, 480 gms. of sodium bicarbonate, and 960 gms. of tricaltsate were given in

45 days. Because of pyloric obstruction, a gastroduodenostomy was performed on the thirty-ninth day, from which the patient made an uneventful recovery. Studies of the acid-base balance revealed the presence of a severe alkalosis (see Table 4). On the twenty-seventh day, the patient developed a flexor spasm of both forearms and hands, and numbness of the face; the Chvostek sign was positive. Three thousand cc. of 5% glucose in normal saline were given parenterally and the patient recovered promptly. It will be noted that the acid-base balance at this time was practically normal. The serum calcium, however, was markedly lowered but returned to normal within seven days. Two of ten urine specimens contained a trace of albumin; the specific gravity ranged from 1005 to 1022. The patient took alkalis regularly for the next two years but entered the hospital a third time (12/31/37-1/21/38), 35 months after the initial visit, because of recurrent hemorrhage. She had been vomiting for nine days before admission. Three hundred and thirty grams of calcium carbonate and 900 gms. of sodium bicarbonate were given in 31 days. The acid-base balance on the third day was normal; the blood urea nitrogen measured 11.1 mg.% and the urea clearance 42% of average normal. Eighteen days later there was a slight rise in the serum CO_2 (32 mM/L) and pH (7.56); the blood urea nitrogen now measured 23.6 mg.% and the urea clearance 22%. On the twenty-ninth day, however, the acid-base balance was normal; the blood urea nitrogen was 12.1 mg.%, and the urea clearance 60%. Seven urine examinations were negative; the specific gravity ranged from 1008 to 1016. Alkali therapy was continued subsequently for almost two years. The patient vomited frequently.

The fourth hospital admission occurred five years and ten months after the original entry (11/5/40-11/23/40). The blood pressure at this time was 170/94. Wangensteen aspiration of the stomach was carried out for ten hours each day. Three thousand cc. of 5% glucose in distilled were administered parenterally daily. This program was discontinued after five days and on the seventh day salt was added gradually to the regimen. Eighty-eight grams of calcium carbonate were given in the last four days of this hospital period. A trace of albumin was noted in one of six urine specimens; the specific gravity ranged from 1011 to 1014. Numerous studies of the acid-base balance were made (see Table 5). The patient vomited frequently during the next month.

She was readmitted for the last time on 12/28/40 in a semicomatose condition. The reflexes were hyperactive and there were coarse, fibrillary, muscular twitchings. The serum chloride measured 71 mM/L, the serum CO_2 48.5 mM/L, and the pH 7.70. Fifteen hundred cc. of normal saline were given parenterally to no avail. The patient developed clonic convulsions and she died several hours later.

Necropsy revealed an acute gastric ulcer with high-grade stenosis of the pylorus; a chronic duodenal ulcer with high-grade stenosis of an old gastroduodenostomy and perforation into the head of the pancreas; recent hemorrhage throughout head of pancreas; recent hemorrhage and edema of lungs. Two parathyroid glands were normal grossly and histologically.

The left kidney weighed 100 gms.; the capsule stripped with moderate difficulty, leaving a diffusely granular, pale surface. The cortex measured 4-6 mm. and the medulla 14-15 mm. The cortical rays were distinct; the pyramids were slightly hyperemic. The renal pelvis was normal; there was one recent subcapsular hemorrhage. The right kidney weighed 112 gms. and its appearance was essentially similar to that of the left kidney. Microscopic examination revealed an increase in fibrous tissue and a few fine cortical scars with foci of round cells near the capsule. A few glomeruli were completely hyalinized and many others showed some degree of sclerosis chiefly due to an increase in hyaline ground substance. In occasional glomeruli there was marked thickening of the basement membranes. The tubules varied considerably in appearance. Some were widened and lined by flat cuboidal cells; others possessed epithelium with hyperchromatic nuclei of varying size and form, and mitotic figures were seen occasionally, indicating active cell proliferation. There was extensive desquamation of the epithelium in some of the distal collecting tubules and the lumina often were completely obstructed by loose epithelial cells and granular, protein debris. Hyaline casts were few in number. Many collecting tubules were filled with coarse, blue-staining or almost colorless, granular masses which stained black with the Kossa stain (Fig. 3), indicating that they were composed of calcium. The epithelium of these tubules was necrotic. Foci of interstitial inflammation were noted surrounding the calcium-filled tubules. Some arterioles had thickened hyaline walls but many of the vessels showed little change. The Gomori (10) stain revealed a markedly decreased alkaline phosphatase content of the kidney.

Comment.--Although the kidneys in Case 1 showed acute and chronic degenerative changes, most of the renal parenchyma was normal. Calcium precipitate was present in occasional collecting tubules. A few tubules were completely obstructed by these masses and their epithelium presented mild degenerative changes. Similar but less marked findings were noted in Case 2 in which the alkalosis also had been severe. The kidneys in Case 3 showed the

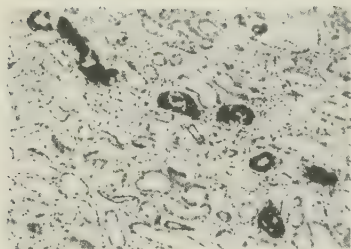


Fig. 3.--Photomicrograph demonstrating presence of calcium precipitate in renal collecting tubules in Case B. G.

typical findings of nephrosclerosis secondary to malignant hypertension. The changes in the tubules are attributable to the passive congestion. None of the findings could be related to the alkali therapy or alkalosis. Case 4 was of great interest, not only because this patient had taken large quantities of alkali for six years, but also because of the prolonged and excessive depletion of chloride through vomiting and gastric aspiration. She had experienced one episode of mild alkalosis and three bouts of severe alkalosis. Although considerable renal damage was visible, much of the parenchyma appeared fairly normal. Many of the changes, i.e., hyalinization of the glomeruli, tubular atrophy, increased fibrous tissue, and arteriolar thickening, are attributable to the hypertension which had been present. The precipitation of calcium in the lumina of the collecting tubules with obstruction of some of these tubules was more extensive in this case than in any other of the entire series. The histologic findings resemble those of an interstitial pyelonephritis seen in patients not given alkalis; this possibility must be considered even in the absence of a suggestive history (11).

It is important to note that all patients of this group had vomited excessively and that all but one individual had had a hypertension.

DISCUSSION

The most frequent histologic finding in the kidney noted in this study was the presence of calcium precipitate in the collecting tubules. Some of these tubules were obstructed by the calcium masses and their epithelium showed both degenerative and regenerative changes. This finding was present in three patients who had previously experienced an alkalosis but who did not die during the acid-base disturbance and in three individuals in whom alkalosis was present at the time of death. All six patients had lost excessive amounts of chloride either by vomiting or gastric aspiration.

The precipitation of calcium in the collecting tubules of the kidney is of considerable interest, although in the present study it did not appear to be of sufficient severity as to destroy the function of more than a relatively few nephrons. It is not a specific complication of "alkali alkalosis." It was first described by Nazari (12) in 1904 in two patients with vomiting secondary to pyloric stenosis. Many writers (13) subsequently emphasized its occurrence in individuals with pyloric and upper intestinal obstruction, none of whom had received alkalis. It has been observed also in the kidney of the dog after a prolonged and severe chloride depletion (cf. Part VI). Similar changes have been found after alkalosis secondary to continuous gastric aspiration as in the following case which had never received alkali:

T. W. (Unit no. 103687), a 50-year-old man, entered the hospital with peritonitis following the rupture of a gangrenous appendix. Because of abdominal distention, he was treated by continuous Wangensteen aspiration. Alkalosis developed despite the administration of saline solution, and the patient subsequently died of cardiac failure and bronchopneumonia. The blood chloride which had decreased to 214 mg.% rose to 436 mg.% after the use of saline infusions; the CO_2 measured 28.3 mM/L, while the pH varied from 7.54 and 7.59. The blood urea nitrogen was extremely high, measuring 231 and 256 mg.%; the blood creatinine was also elevated to an unusual degree, measuring 6.75 and 7.0 mg.%. Microscopic examination of the kidney revealed the presence of blue-staining material, probably calcium, in many of the collecting tubules.

The epithelium of these tubules showed degenerative changes. There were numerous foci of interstitial inflammation; considerable protein debris as well as numerous casts were present in the lumina of the tubules. The histologic findings were identical with those observed in the six patients previously described.

The mechanism of this condition is not entirely clear.

Calcium may be deposited in necrotic cells. The renal parenchyma often is normal, however, and the process may occur too rapidly for extensive necrosis to have taken place. Kerpel-Fronius and Martyn (4) produced salt deficiency in cats by ligation of the pylorus and noted calcium precipitation only in those animals in whom both dehydration and alkalosis occurred; in the cats in which the development of alkalosis was prevented, only fat degeneration of the tubules was observed. Hatano (15) was able to prevent this complication during experimental hypochloremia by the intravenous injection of sodium chloride, further emphasizing the importance of chloride depletion in this process. Deposition of calcium in the kidney after alkalosis is due apparently to an alteration in the physical chemical state of the urine resulting presumably in the precipitation of calcium phosphate and calcium carbonate. Enzymes such as alkaline phosphates probably play no role in its development (16). Zeman and his associates (13) studied the process in cats in which alkalosis was allowed to develop after ligation of the pylorus. The presence of calcium in the kidney was noted within 48 hours. Gömöri and Sarmai (17) later confirmed this observation and demonstrated that it was a reversible process, the calcium disappearing rapidly after removal of the pyloric obstruction.

SUMMARY

No special histologic changes were noted in the glomeruli of the kidney in 14 patients after prolonged alkali therapy with and without alkalosis. The epithelium of the collecting tubules in six of the patients studied showed degenerative and regenerative changes. Precipitation of calcium was noted in the lumina of these tubules. The tubules which did not contain calcium usually appeared normal. Three of these six patients had previously experienced an alkalosis but did not die during the acid-base disturbance; alkalosis had been present at the time of death in the

other three cases. All six patients had lost excessive amounts of chloride by vomiting or therapeutic aspiration. Similar findings were observed in a patient not receiving alkali but in whom a severe hypochloremia and alkalosis developed as a result of gastric aspiration.

CONCLUSION

The long-continued administration of alkali in man with or without alkalosis does not lead to significant anatomic change in the kidney attributable to alkali.

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TABLE 1

ACID-BASE BALANCE AND UREA CLEARANCE IN CASE W. R.

Hospital Day	Serum Cl mM/L	Serum CO ₂ mM/L	pH	B.U.N. mg. %	Urea Clearance % Avg. Normal
120th	100.2	39.0	7.53	15.1	79
137th	92.1	36.1	7.52	14.9	91
141st	90.5	35.3	7.46		..
152nd	84.3	45.8	7.53		..
153rd		43.2	7.48	19.7	..
162nd	88.6	32.6	7.47	16.1	61
164th	100.8				..
168th	88.4	33.4	7.47	40.4	..
172nd	93.8	30.4	7.43		..
179th	94.1	33.5	7.50	9.2	87
183rd	91.4	33.3	7.50	10.1	63
186th		34.0	7.50	9.1	80
190th		36.2	7.57	14.6	..
193rd	88.0	37.4	7.53	17.4	102
200th	89.0	35.0	7.48	25.0	73
207th	95.0	26.4	7.41	43.9	41
210th	92.3	23.4	7.33	63.5	..
211th	died				

TABLE 2

ACID-BASE BALANCE AND UREA CLEARANCE IN CASE S. S. M.

Hos- pital Day	Serum Cl mM/L	Serum CO ₂ mM/L	pH	B.U.N. mg.%	Urea Clear- ance % Avg. Normal	N PN mg.%	Creat- inine mg.%	Total Base m.Eq./L
3rd	94.0	30.7			..	53.6		
4th				40.7	15			
10th	72.0	45.0	7.62	65.1	..		3.37	
14th	86.0	38.1	7.63	45.2	10			
18th	97.8	32.9	7.52	43.5	22			
21st		30.0	7.53	38.8	16			
23rd	posterior gastroenterostomy and cholecystectomy							
48th	98.8	24.9	7.47	17.8	22			
60th	98.0	26.4	7.34	20.4	37			
66th	97.6	22.8	7.32	27.3	33			138.6
73rd	98.2	20.4	7.38	26.6	30			
75th		16.7			..			
77th	96.3	16.8			..			140.6
79th		10.1			..	42.5		died

TABLE 3

ACID-BASE BALANCE IN CASE J. P. B.

Hospital Day	Serum Cl mM/L	Serum CO ₂ mM/L	Serum pH
4th	81.4	45.6	
6th	70.0	57.1	7.50-7.58
7th	72.6	55.5	
8th	78.0	48.8	
9th	147.0(?)	30.9	7.38

TABLE 4

ACID-BASE BALANCE AND UREA CLEARANCE IN CASE B. G.

Hospital Day	Serum Cl mM/L	Serum CO ₂ mM/L	pH	B.U.N. mg.%	Urea Clearance % Avg. Normal	Ca mg.%	P mg.%
7th		62.1	7.65		..	...	...
8th		50.5	7.58		..	...	...
10th		36.0	7.53		..	...	...
14th		36.6	7.52		..	...	...
17th	83.7	37.4	7.52		..	...	...
21st	101.5	35.4	7.50	28.2	..	...	...
22nd				25.4	22	...	...
28th	99.1	32.6	7.49		..	6.2	...
30th					..	7.5*	...
32nd				95	52	...	...
35th	79.0	46.0	7.49		..	9.8	...
49th					..	9.9	3.9

*Plasma protein = $6.4 \text{ gm.}\% - A/6 = 5.12/1.28 = 4.00$.

TABLE 5

ACID-BASE BALANCE IN CASE B. G. (SUBSEQUENT VISIT)

Hospital Day	Serum Cl mM/L	Serum CO ₂ mM/L	pH	B.U.N. mg.%	Serum Ca mg.%
2nd	95.9	39.4	7.54	9.6	...
3rd				21.5	...
5th	87.6	35.6	7.58	...	...
6th	86.8	35.1	7.61	...	...
7th	80.0	41.2	7.60	...	...
10th	56.7	41.3	7.47	18.6	...
11th	64.3	37.4	7.67	...	...
12th	80.1			9.4	...
14th	86.2	37.2	7.53	6.1	8.9
15th				8.8	...
16th	92.6	37.0	7.52	...	...

PART VIII. SUMMARY

SUMMARY

The general survey of the case histories of patients developing alkalosis during the Sippy treatment of peptic ulcer disclosed a number of fairly typical features: The symptoms usually appeared within four to ten days after the onset of therapy. They consisted chiefly of a distaste for the milk and cream and alkali, weakness, dizziness, headache, nausea, and vomiting. The acid-base disturbance was characterized chemically by a decrease in the serum chloride and by a rise in the serum CO_2 and pH. The intensity of the alkalosis could not be correlated with the quantity of alkali administered; the electrolyte disturbance seemed to be more severe, however, in patients with gastric retention. The role of the kidney in the pathogenesis of the acid-base disturbance was difficult to evaluate. Alkalosis was seen in many patients with low urea clearances, but it was observed also in individuals with no evidence of renal disease. The serum electrolytes remained normal, furthermore, in numerous patients with renal impairment. A decrease in renal function was noted frequently during alkalosis, especially in those individuals with severe alkalosis and with pre-existent renal disease. The urea clearance invariably returned to its original level, however, after the acid-base balance was restored. Similarly, no permanent decrease in the urea clearance was observed after the long continued administration of alkali. Inasmuch as it was not possible on the basis of the available information to evaluate completely the mechanism of the alkalosis seen in these patients, a study was undertaken of the factors considered most likely to be involved in the acid-base disturbance, namely, (1) the effect of a soluble alkali such as sodium bicarbonate, (2) the effect of a relatively insoluble alkali such as calcium carbonate, (3) the role of chloride loss, and (4) the role of the kidney.

Acute sodium bicarbonate alkalosis was produced in the dog by the intravenous injection of varying quantities of this alkali. The unusually severe chemical disturbance so induced was characterized by a marked increase in the sodium and total base

and by a corresponding rise in the bicarbonate content of the blood. No significant change occurred in the serum chloride, calcium, and phosphorus. Acute sodium bicarbonate alkalosis was not investigated in man. A study was made, however, of the effect of the prolonged administration of massive amounts of this alkali on the acid-base balance and urea clearance. It was found that the serum electrolytes remained normal except for slight increases in the serum CO_2 and pH and that the urea clearance remained unimpaired despite the ingestion of 32,000 gms. of sodium bicarbonate over a period of twenty months. The remarkable tolerance for alkali exhibited by this patient was attributed to the excellent renal function and to the large quantities of water taken daily.

A clinical study subsequently was undertaken of the effect of calcium carbonate on the acid-base balance. One hundred and five patients were placed on regular ulcer management, except that calcium carbonate, in doses averaging 30 gms. daily, was given instead of the usual sodium bicarbonate-calcium carbonate mixture. The electrolyte disturbance, which occurred in 32 of this group, consisted of a diminution in the serum chloride and a rise in the CO_2 and pH; the serum calcium and phosphorus were normal and the total base was not elevated. Although a decrease in the urea clearance was noted frequently during alkalosis, renal function invariably returned to original levels after the restoration of the acid-base balance. The interpretation of the alterations in the serum electrolytes was complicated by the fact that loss of chloride resulting from vomiting or the aspiration of gastric juice had occurred in all cases. The possibility thus arose that the alkalosis might have been due entirely to chloride loss and that the addition of adequate quantities of salt to the regimen might correct the acid-base disturbance despite the continued ingestion of alkali. Additional sodium chloride, therefore, was administered orally to a group of patients with alkalosis, the alkali (calcium carbonate) being continued. Clinical improvement occurred rapidly in all cases and was accompanied by a complete recovery of the acid-base balance. The urea clearance likewise returned to its original level in those patients in whom it had decreased. In view of these findings, a study was undertaken to determine the frequency of alkalosis when sodium chloride was administered simultaneously with the alkali. This investigation

was carried out in a series of 150 patients with equally striking results. The incidence of alkalosis diminished from 30 to 10%. The alterations in the serum electrolytes which did occur were usually mild, and were corrected in practically all cases by a further increase in the salt intake in spite of the continued administration of calcium carbonate.

These results seemed to indicate that loss of chloride was the major factor in the acid-base disturbance. However, the evidence did not exclude calcium carbonate as a primary cause of alkalosis in some cases. It was thought that this alkali might remove a large amount of chloride from the gastric juice, some of which was not reabsorbed. Another possibility, despite the normal values for total base, was that absorption of bicarbonate into the blood may have occurred. It seemed desirable, therefore, to investigate the action of calcium carbonate on mineral excretion. Detailed studies consequently were obtained in three patients before, during, and after the administration of this alkali. Calcium carbonate was given in amounts similar to those employed in the Sipsey program, 20 gms. daily. The salt intake was maintained at a constant moderate level; the patients were not aspirated. The effects of two other non-absorbable compounds, aluminum phosphate and aluminum hydroxide, were studied for comparison. It was found that calcium carbonate decreased the acidity of the urine, and in some cases, its chloride content also. Phosphate excretion was diverted to a considerable extent from the urine to the bowel. The urinary calcium rose, while the potassium content decreased slightly. Large quantities of aluminum phosphate did not affect mineral excretion appreciably. Large amounts of aluminum hydroxide altered mineral excretion in a manner similar to but somewhat less marked than that of calcium carbonate. All three compounds increased the output of chloride in the feces to a similar degree; chloride loss by this route was very slight, however, and obviously unimportant. The alterations in mineral excretion were relatively mild and neither calcium carbonate, aluminum phosphate, nor aluminum hydroxide produced clinical or chemical alkalosis. These studies, while not absolutely excluding calcium carbonate as a factor, indicated, nevertheless, that the alkalosis of calcium carbonate administration was not attributable in the vast majority of instances to the alkali per se.

The importance of chloride loss in alkalosis thus became

even more clear and led to a detailed investigation of the effect of hypochloremia on the serum electrolytes and the kidney. This problem was studied first in dogs in which a gradual but severe depletion of body chloride was produced by the intermittent withdrawal of gastric juice through a gastric fistula. The chloropenia was found to be accompanied by a marked increase in the serum CO_2 and pH. There was no significant elevation of the blood urea nitrogen and the urea clearance remained normal. No evidence of renal injury could be detected on histologic examination of the kidney. Precipitation of calcium was noted in some of the renal collecting tubules in one dog, and was attributed to an alteration in the physical chemical state of the urine induced by the prolonged loss of chloride. The changes in the acid-base balance noted in these animal experiments were quite similar to those observed in the clinical studies. However, no impairment of renal function had been observed in the dogs, while the urea clearance often had temporarily decreased in the patients. This apparent variation in the response of the kidney to similar changes in the serum electrolytes seemed to be related to the fact that the dogs had received large amounts of water daily, whereas many of the patients had lost fluid as a result of vomiting and gastric aspiration. The return of the urea clearance to original levels, despite continued ingestion of alkali, likewise could be attributed to the greater intake of fluid induced by the added sodium chloride.

In an effort to confirm these observations made in the dog, a study of the effect of hypochloremia was undertaken in man. Depletion of chloride was produced by the aspiration of gastric juice for varying lengths of time. A rapid loss of chloride first was induced in two patients. The appearance of shock in these individuals and the prompt subsidence of symptoms after the injection of saline solution simulated closely the clinical manifestations of an Addisonian crisis. A less acute depletion of chloride was accomplished in two adult men in whom large quantities of glucose and water were administered parenterally each day. The acid-base disturbance in these cases was characterized by a marked decrease in the serum chloride, sodium, and total base; and by a rise in the CO_2 and pH. The serum calcium, phosphorus, and potassium remained normal. As in the dog, no significant elevation of the blood urea nitrogen or lowering of

the urea clearance was observed. Since considerable amounts of water had been given daily, it appeared, in both the animal and human experiments, that dehydration did not exist in the sense of deprivation of water, although it was present in the sense that loss of body fluid accompanied the loss of electrolyte. These studies indicated (1) that depletion of chloride by the withdrawal of gastric juice could lead to a severe alkalosis not unlike the acid-base disturbance encountered during Sippy management, (2) that the loss of chloride was accompanied by a loss of sodium, and, therefore, of extra cellular fluid, and (3) that a relative state of hydration could be maintained, despite loss of electrolyte, by the daily administration of large amounts of water which, though not lessening the severity of the alkalosis, apparently could prevent nitrogen retention and a diminution in the urea clearance.

Inasmuch as no permanent decrease in the urea clearance had been observed after alkalosis or long-continued alkali therapy, it did not seem likely that either alkalosis or alkali ingestion produced significant anatomic changes in the kidney. This problem was investigated more directly in the dog by histologic examination before and after the prolonged use of sodium bicarbonate. One kidney was removed prior to the experiment for control study. Despite the fact that massive amounts of alkali had been administered, the appearance of the "alkali" kidney did not differ significantly from that of the control. A study was made also of the autopsy findings in patients who, during life, had received large amounts of alkali. No unusual findings were observed in four individuals in whom the acid-base balance had been normal. Calcium precipitate was noted in the renal collecting tubules in six patients, three of whom had previously experienced an alkalosis but had died of other complications and three individuals in whom alkalosis was present at the time of death. Some tubules were obstructed by the calcium deposits and their epithelium showed both degenerative and regenerative changes. The glomeruli, and the tubules which did not contain calcium, usually appeared normal. All six patients in whom these changes were noted had lost excessive amounts of chloride either by vomiting or therapeutic aspiration. Similar histologic findings were observed in a man, not receiving alkali, but in whom a severe hypochloremia and alkalosis developed after the continued withdrawal of gastric

juice and also in a dog after a prolonged depletion of chloride. The precipitation of calcium and the changes secondary thereto were attributed to an alteration in the physical chemical state of the urine resulting from the hypochloremia. The results of these anatomic studies, therefore, were in complete agreement with the clinical observation that alkali per se did not produce renal injury.

PART IX. CONCLUSIONS

CONCLUSIONS

1. Alkalosis is a not infrequent complication of peptic ulcer and, indeed, of any obstructing gastroduodenal lesion, with or without treatment.

2. The mechanism of the alkalosis consists of (a) the absorption of soluble alkali and (b) the loss of gastric chloride.

3. The alkalosis induced by soluble alkali, e.g., sodium bicarbonate, is characterized by an increase in the sodium, total base, pH, and carbon-dioxide content of the blood. This type of alkalosis does not develop if (a) renal function is normal, and (b) the amount of water supplied daily is sufficiently great to eliminate the base as rapidly as it is absorbed.

4. The alkalosis seen with calcium carbonate administration is usually, if not exclusively, attributable to the loss of chloride resulting from gastric aspiration or emesis coupled with an inadequate intake of salt.

5. (a) Calcium carbonate in moderate amounts decreases the acidity of the urine and, in some cases, its chloride content also. The urinary calcium is increased. Phosphate excretion is diverted to a considerable extent from the urine to the bowel. There is a slight but unimportant loss of chloride in the feces.

(b) Large amounts of aluminum phosphate do not affect mineral excretion significantly.

(c) Large amounts of aluminum hydroxide alter mineral excretion in a manner similar to but less marked than that of calcium carbonate.

(d) These changes in mineral excretion are relatively mild and are not associated either with clinical or chemical alkalosis.

6. In this work, no conclusive evidence has been obtained to indicate that calcium carbonate, in the absence of chloride loss, produces alkalosis.

7. The loss of gastric chloride can produce either an acute or chronic alkalosis characterized chemically by a decrease in the serum chloride, sodium, and total base, and by an elevation

of the pH and the bicarbonate content of the blood.

8. Azotemia and impairment of renal function do not occur during the alkalosis of hypochloremia provided the supply of water is adequate.

9. Acute hypochloremia may produce a clinical picture which is similar to that observed in the crisis of adrenal insufficiency.

10. Alterations in renal function are a by-product of these disturbances in the serum electrolytes and are not causal in the production of alkalosis.

11. The prolonged administration of alkali with and without alkalosis does not produce detectable anatomic changes in the kidney. The prolonged depletion of chloride may lead to a deposition of calcium in the renal collecting tubules, attributable to an alteration in the physical chemical state of the urine.

12. The clinical syndrome of alkalosis observed with gastric disease results from an alteration in the electrolyte composition of the blood serum produced by (a) the absorption of soluble alkali, (b) the loss of gastric chloride, or (c) a combination of the two.

